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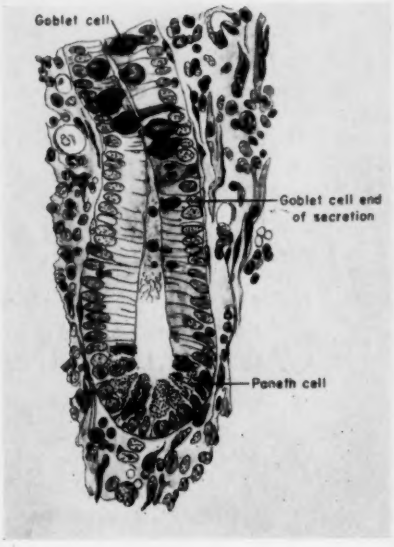

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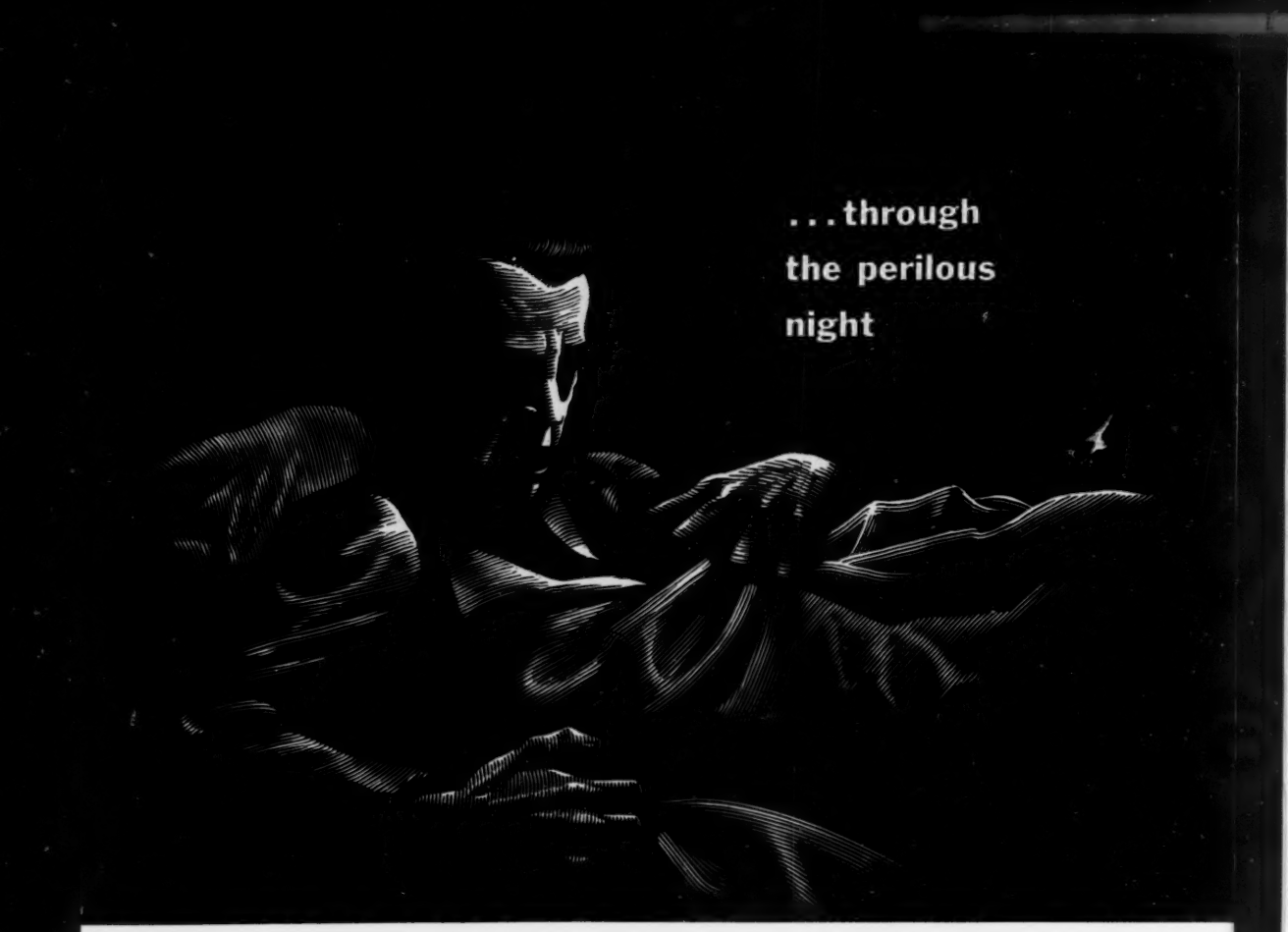

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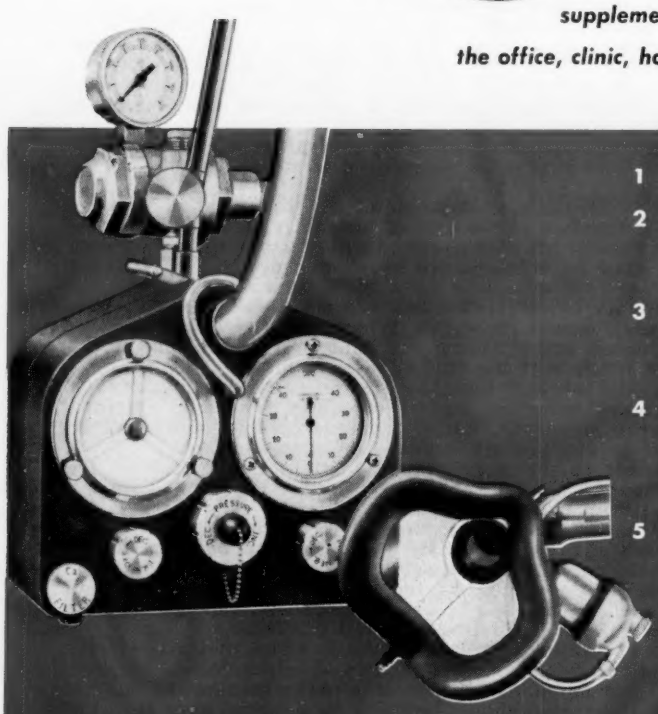

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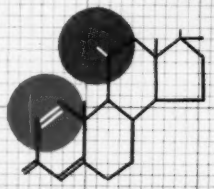

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Nitrofurantoin

Clinical and Laboratory Studies in Urinary Tract Infections

WILLIAM A. RICHARDS, M.D.
EGON RISS, M.D.
EDWARD H. KASS, M.D., Ph.D.
and
MAXWELL FINLAND, M.D., Boston

Nitrofurantoin,* N-(5-nitro-2-furfurylidene)-1-aminohydantoin, is one of a series of substituted furan derivatives having a nitro group at the 5- position in the furan ring and possessing antibacterial properties.† It is the first of this series of compounds to be used in human infections. After oral administration it appears in significant concentrations only in the urine ‡; its usefulness has, therefore, been limited to infections of the urinary tract, for which it has been used by a number of workers.§

Dodd and Stillman,[17] in 1944, showed that the addition of a nitro group in the 5- position to a large number of substituted furan derivatives markedly enhanced their antibacterial properties. Cramer and Dodd [18] extended these studies and showed that the action of compounds of this type is bacteriostatic but that under certain circumstances, or at higher concentrations, some of them may also be bactericidal. Enhancement of the antibacterial effect in simple synthetic media, and the impairment of this effect by the addition of serum or blood suggested an antimetabolite action.‖ Nitrofurantoin was not among the compounds reported by these authors, and there are no published growth curves using this analogue, although nitrofurantoin is stated by the manufacturer to be bacteriostatic—and, in higher concentrations, bactericidal.[19] It is also stated that this compound retains its effectiveness in the presence of serum and pus. Mintzer and co-workers [1] observed only slight reduction of its antibacterial effect by nicotinic acid, feces, and pus, and no effect from a number of other substances.

The low solubility of the 5-nitro furans in aqueous systems is a limiting factor in in vitro studies and also in their use systemically. The solubility curve for nitrofurantoin in urine in vitro at 37 C and at different pH levels, as given by the manufacturer,[19] shows a marked increase with increasing pH; thus, the solubility at pH 4.0 is shown to be 22 mg. per 100 ml.; at pH 6.0 it is 30 mg., and, when extrapolated, it is 90 and 230 mg. per 100 ml. at pH 7.0 and 7.7, respectively.[19]

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Aided by a grant from the U. S. Public Health Service.

From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.

* Supplied under the trade-mark Furadantin by Eaton Laboratories, Norwich, N. Y.

† The first report of the isolation of nitrofurantoin was made by Paul, H. E.; Hayes, K., and Bender, R. C.: Urinary Excretion Studies with Furadantin (N- [5-Nitro-2-Furfurilidine] 1-aminohydantoin) and Selected Nitrofurans, read before Section C (Chemistry) of the American Association for the Advancement of Science, Boston, Dec. 27, 1953.

‡ References 1 and 2.

§ References 1-16.

‖ References 17 and 18.

Polyethylene glycol 300 has been used in some previous in vitro studies,¶ to obtain solution of nitrofurantoin.

The present studies have avoided the use of this or similar solvents but have relied on the inherent solubility of the drug on the substrates that were used. Observations were made on the effect of pH on the antibacterial action of nitrofurantoin. Concentrations in blood and urine were estimated by the antibacterial action rather than spectrophotometrically by the ultraviolet absorption technique advocated by Paul and his associates.[20] These and other in vitro studies, together with clinical observations of the use of nitrofurantoin in urinary tract infections, are presented here.

CLINICAL AND BACTERIOLOGICAL OBSERVATIONS

Patients Studied.—Thirty-nine hospitalized adults with urinary tract infections were treated with nitrofurantoin in doses of 100 to 200 mg. four times daily (7 to 10 mg. per kilogram of body weight per day) for periods ranging from 2 to 13 days and averaging 7 days. One patient was studied during two widely separated episodes. Therapy was discontinued in some cases when bacteruria was unaffected, but in no instance after less than 48 hours. The patients ranged in age from 14 to 93 years; 12 were less than 50 years old, 11 were 50 to 69 and 16 were 70 or over. The diagnosis of urinary tract infection was based on the demonstration of bacteruria and pyuria, with organisms seen in Gram-stained smears of freshly voided, unspun urine and corroborated by finding plentiful growth in cultures on routine media. Specimens obtained by catheter were examined in each instance in females, and clean-voided or catheterized specimens in males.

In 28 of the 39 patients the site of the infection in the urinary tract was not definitely determined. In 10 patients, a diagnosis of acute pyelonephritis was made on the basis of an acute febrile course and flank pain or by pathological examination; 5 of these 10 had a history of recurrent episodes of acute pyelonephritis, and in 3 others persisting bacteruria and pyuria suggested the diagnosis of underlying chronic pyelonephritis. In eight patients, however, there was direct evidence of chronic upper urinary tract involvement, and two had gross abscess formation in the kidneys (observed at operation in one and at necropsy in the other). Bacteremia was demonstrated in three cases.

¶ References 2 and 15.

In 12 of the 39 patients no definite complicating conditions were recognized, but among these 12 there were some abnormalities of questionable significance. However, studies designed to determine possible complicating conditions were incomplete in some instances. The complications that were recognized included the following:

	Cases, No.
Prostatic hypertrophy, varying from asymptomatic enlargement to complete obstruction	7
Previous prostatic surgery	7
Prostatic carcinoma with bleeding per urethra	1
Urethral strictures	2
Staghorn calculus	1
Ureteral stones	2
Partial ureteral obstruction with hydronephrosis and hydroureter	2
Pregnancy (third trimester, 1, and recent abortion, 1)	2
Associated tuberculosis of urinary tract	1
Vesicovaginal and rectovaginal fistula	1
Diabetes (in addition to other complications)	7
Indwelling catheter during treatment	4

Catheterization or other instrumentation preceded the onset of infection in several instances.

No other antimicrobial agent was given while the nitrofurantoin was being administered, except in one patient who was receiving penicillin for osteomyelitis before the urinary tract infection was recognized and in whom this was continued during and after the course of nitrofurantoin. Ten other patients had received other antimicrobials for the same episode either immediately or within a few days before the nitrofurantoin was started. The previous therapy consisted of a sulfonamide alone in one and given with penicillin in three, these two agents and a tetracycline antibiotic in one, and the latter alone in five. Antibiotics to which the infecting strains were sensitive were used to continue therapy, either immediately or after an interval, in five of the patients in whom the infection was not controlled by nitrofurantoin.

Microscopic examinations and cultures of urine were repeated during the course of treatment and, when possible, at least 48 hours after treatment was stopped, if clearing had been accomplished during treatment. No follow-up observation of recurrent infection was accepted if any instrumentation was performed in the interval following treatment. In many cases in which clearing of the urine of bacteria was demonstrated by Gram stain during or after treatment, bacterial counts were performed with cultures of freshly voided urine specimens to determine how thoroughly the bacteruria had cleared.

Clinical Results.—The patients were observed for the effect of therapy on fever,

TABLE 1.—*Clinical Effectiveness of Nitrofurantoin in Forty Cases of Urinary Tract Infections*

Pre-Therapy Bacteriology		Symptoms Subsided Completely During Therapy				Partial Improvement During Treatment	No Clinical Improvement During Treatment	Symptomless Bacteriuria
Organism	Cases, No.*	Cases, No.	No Post-Therapy Recurrence	Recurred Post-Therapy	No Post-Therapy Follow-Up			
E. coli	17 (4)	11 (2)	6 (1)	4 (1)	1	3	1 (1)	2 (1)
A. aerogenes †	13 (3)	5	2	2	1	2	6 (3)	0
Enterococcus	3 (2)	1 (1)	1 (1)	0	0	1	1 (1)	0
Proteus	11 (6)	3 (1)	2 (1)	1	0	1	7 (5)	0
P. aeruginosa	3 (2)	0	0	0	0	1	2 (2)	0
Viridans Streptococcus	3 (3)	2 (2)	0	1 (1)	1 (1)	0	0	1 (1)
S. albus	1 (1)	1 (1)	0	0	1 (1)	0	0	0
S. aureus ‡	1	0	0	0	0	0	1	0
Total cases	40 (9)	19 (3)	9 (1)	7 (1)	3 (1)	8	11 (5)	2 (1)
Organisms in cases without recognized complications	12 (1)	8 (1)	4 E. coli 1 A. aerogenes 1 E. coli, Enterococcus & Proteus	1 E. coli	1 E. coli	1 E. coli 1 Enterococcus	1 Proteus	1 E. coli
Organisms in acute pyelonephritis								
Uncomplicated	3 (1)	2 (1)	1 E. coli, Enterococcus & Proteus	1 E. coli		1 Enterococcus		
With complications	7 (2)	3 (1)		1 E. coli 1 E. coli & Viridans Streptococcus	1 A. aerogenes	1 P. aeruginosa	1 A. aerogenes † 1 A. aerogenes & Proteus	

* Numbers in parenthesis indicate cases with mixed infections (six with two organisms and three with three).
† Includes one case with Klebsiella pneumoniae Type C identified before treatment, but subsequent isolations did not react with specific antiserum.
‡ Not hemolytic.

pyuria, and leucocytosis and on such urinary tract symptoms as flank pain, dysuria, urgency, and frequency. Table 1 records a summary of clinical results analyzed according to the initial infecting organisms. The results in the 12 cases without recognized complications and in the 10 diagnosed as acute pyelonephritis are also listed separately. Only 1 of 17 infections with Escherichia coli failed to show any improvement during treatment, whereas in 6 of 13 cases of infection with Aerobacter aerogenes and 6 of 9 cases with Proteus infection there was no improvement. Of the 12 patients without recognized complication, only 1 failed to show any improvement (an 82-year-old woman with a Proteus infection in whom no special urologic studies were done) and 8 showed complete subsidence of the clinical manifestations while on treatment. No consistent effectiveness was noted in the cases of acute pyelonephritis.

Bacteriologic Results.—The effect of treatment was noted on 50 strains identified before the onset of therapy. Table 2 indicates the results in all the cases according to species; the results in the cases without recognized complications and in those with acute pyelonephritis are also shown separately. The heading "Cleared on Treatment" indicates that at least one culture was entirely free of the organism in question during the course of treatment; "Not Cleared on Treatment" means that the organism remained evident by Gram stain as well as culture, implying the presence of 100,000 or more organisms per milliliter [21] "Not Cleared, but $<10^4$" indicates that bacteria persisted in numbers less than 10,000 per milliliter during treatment, but in every one of these cases the organisms were again evident by Gram stain of unsedimented urine and shown to be in excess of 100,000 per milliliter after cessation of treatment.

As shown in Table 2, only E. coli was cleared during treatment and remained cleared after treatment was stopped in a majority of the cases. Moreover, E. coli was not demonstrated as a new organism in any of the patients after treatment was started.

TABLE 2.—*Bacteriological Effect of Nitrofurantoin on Fifty-Two Strains Isolated from Forty Cases of Urinary Tract Infections*

Organism	Strains Isolated Before Therapy	Negative Cultures During Therapy	Heavy Growth During Therapy	Not Cleared, but <10^4 Organisms/Ml. During Therapy	Results of Post-Treatment Follow-Up: Negative Cultures >2 Days	Results of Post-Treatment Follow-Up: Organism Recurred	Results of Post-Treatment Follow-Up: No Follow-Up	Appeared as New Infecting Organism During Therapy
E. coli	17	15	1	1	9	2	4	0
A. aerogenes *	13	5	6 *	2	3	0	2	1
Enterococcus	3	2	1	0	0	1	1	1
Proteus	11	4	4	3 †	0	1	3	2
P. aeruginosa	3	0	3	0	0	0	0	5
Viridans Streptococcus	3	2	1	0	0	0	2	0
S. albus	1	1	0	0	0	0	1	0
S. aureus	1	0	0	1	0	0	0	0
Total strains	52	29	16	7	12	4	13	9
Organisms in 12 cases without recognized complications	14	8 E. coli 2 Enterococcus 1 A. aerogenes 1 Proteus	1 Proteus	1 E. coli	6 E. coli 1 A. aerogenes	1 E. coli 1 Enterococcus 1 Proteus	2 E. coli 1 Enterococcus	0
Organisms in 10 cases of acute pyelonephritis	14	2 E. coli 2 Proteus 1 A. aerogenes 2 Enterococcus	1 E. coli 3 A. aerogenes * 1 P. aeruginosa 1 Viridans Streptococcus	1 E. coli	1 E. coli	2 E. coli 1 Enterococcus 1 Proteus	1 A. aerogenes 1 Enterococcus 1 Proteus	6

* Includes one strain identified as K. pneumoniae, Type C, before treatment, but post-treatment strain did not react with specific antiserum.
† One isolated during treatment of two different episodes in the same patient.

The absence of follow-up data, however, must be taken into account in evaluating the failure of clearing after treatment, particularly with respect to other species. Among uncomplicated cases, 12 of 14 organisms were cleared during treatment and 7 remained cleared after cessation of treatment. Under the heading "New Infecting Organisms" is indicated the appearance of only those new species which occurred in numbers greater than 10,000 per milliliter during or after treatment. During the 40 clinical trials Pseudomonas aeruginosa emerged as a new infecting organism 5 times; Proteus, twice, and A. aerogenes and Enterococcus, each once.

Bacteremia was demonstrated during the second day of treatment with nitrofurantoin in each of two patients. E. coli was found in one of these patients, and A. aerogenes, in the other. In both instances, the organism corresponded to that cultured from the urine prior to treatment.

Untoward Effects.—Nausea and vomiting severe enough to require stopping the medication occurred in only two patients; nine others had less severe degrees of nausea and vomiting. It was not always possible to attribute this effect to the medication; the infection itself or other associated disease may have been responsible. In four patients the nausea and vomiting stopped after the dose was reduced. Two patients had mild diarrhea during treatment. Another patient had vertigo and unsustained nystagmus, which disappeared after the drug was stopped and did not reappear during a brief repetition of the same dose. Nervousness, anorexia, headache, and transient singultus were other complaints associated with treatment.

In two patients a transient failure of erythropoiesis was demonstrated during the nitrofurantoin therapy; in both instances this was manifested by a lack of the expected reticulocytosis in the presence of anemia. One of these patients had sickle-cell-hemoglobin-C disease with a short red cell survival time, and the other had an acute hemolytic episode, either drug-induced or possibly related to the accompanying bacteremia. In neither case could nitrofurantoin be implicated in the failure of erythropoiesis beyond the fact of coincidence; the acute pyelonephritis which was present in each instance may also have played a part. In the case of the acute hemo-

lytic reaction, a reticulocyte response gradually appeared after several days of continued medication with nitrofurantoin.

LABORATORY STUDIES

Susceptibility of Bacteria to Nitrofurantoin

Nearly all the strains isolated from blood and urine of patients in this study were tested for sensitivity to nitrofurantoin. A serial dilution method, employing a standard solution of the drug in urine, broth as the diluent, and either twofold or other step-grade dilutions, was used with these strains. In addition, 16 strains of A. aerogenes and 16 of P. aeruginosa that had been studied for sensitivity to various antibiotics were also tested by the same method, but with use of a broth solution of the drug as a standard. Another group, of 111 strains of various species of Proteus, was tested with an agar plate-dilution method. The sensitivity of these strains of Pseudomonas and Proteus to various antibiotics has been previously reported.#

The standard solutions of nitrofurantoin were obtained without the use of polyethylene glycol or similar agents. The solubility of nitrofurantoin in urine, broth, or nutrient agar at 37 C is in excess of 50 mg. per 100 ml. at pH 7.0. However, the increased solubility of nitrofurantoin with increasing pH is accompanied by a reduction in antibacterial effectiveness, as will be shown later in this paper. In the present observations, the pH of the urine, broth, and agar that were used ranged between 7.0 and 7.4.

The size of inoculum, as shown by others * and confirmed here, also influences the antibacterial action of nitrofurantoin. The inoculum in all the tube-dilution tests was a 2 mm. loopful of a 1 : 100 dilution of a freshly grown culture and contained about 2 to 5×10^5 organisms per milliliter. In the agar-dilution studies, a 1 mm. loopful of a similar culture was streaked on the surface of the agar.

End-points were read in the tube-dilution studies by gross turbidity and on the plates by grossly evident growth. End-points were generally clear and were reproducible from one set of observations to another. This sharpness of end-point and reproducibility was noted even with the arithmetic step-grade dilution schedule used in testing the strains of A. aerogenes.

As would be expected with a primarily bacteriostatic agent, the end-points depended upon length of incubation; hence different ranges of sensitivity are recorded at several incubation times for some of the tests.

Table 3 shows the nitrofurantoin sensitivities of the groups of organisms studied. Strains of E. coli were inhibited by concentrations ranging from 0.4 to 3.2 mg. per

References 22 and 23.

* References 16 and 17.

Table 3.—*In Vitro Susceptibility to Nitrofurantoin of 213 Strains, Mostly from Patients with Urinary Tract Infections*

Species	Strains, No.	Method*	Hours of Incubation	Minimum Inhibiting Concentration, Mg./100 Ml.										Not Inhibited by Highest Concentration Tested			M.I.C. for >⅔ of Strains, Mg./100 Ml.
				0.4	0.8	1.6	2.5	3.2	5.0	7.5	10	12.5	20	12.5	20	50	
E. coli	24†	A	24	2	6	9	..	7	..	..	..	..	..	..	..	..	1.6
Viridans Streptococcus	1†	A	16	..	1	..	..	..	..	..	..	..	..	..	..	..	.....
S. albus	1†	A	16	1	..	..	..	..	..	..	..	..	..	..	..	..	.....
S. aureus	1†	A	16	1	..	..	..	..	..	..	..	..	..	..	..	..	.....
Enterococcus	5†	A	24	1	..	2	2	..	..	..	..	..	..	..	..	..	2.5
A. aerogenes	25†	A	24	..	..	..	2‡	..	6	5	7	4	..	1	..	..	10
	16	B	16	..	..	..	6‡	..	4	4	1	..	1	..	..	..	7.5
			38	..	..	..	4‡	..	2	3	3	3	1§	..	..	..	10
			67	..	..	..	4‡	..	2	3	2	3	2§	..	..	..	10
Proteus, species	20†	A	24	..	..	..	..	..	..	1	..	2	..	17	..	..	>12.5
Proteus mirabilis	66	C	24	..	..	..	..	..	..	..	22	..	39	..	5	..	20
			48	..	..	..	..	..	..	..	15	..	46	..	5	..	20
Proteus morgani	21	C	24	..	..	..	..	..	..	..	21	..	..	..	..	..	10
			48	..	..	..	..	..	..	..	18	..	3	..	..	..	10
Proteus vulgaris	15	C	24	..	..	..	..	..	..	..	11	..	4	..	..	..	10
			48	..	..	..	..	..	..	..	5	..	10	..	..	..	20
Proteus rettgeri	5	C	24	..	..	..	..	..	..	..	2	..	..	..	3	..	>20
			48	..	..	..	..	..	..	..	1	..	1	..	3	..	>20
Proteus, unclassified	4	C	24	..	..	..	..	..	..	..	2	..	2	..	..	..	20
			48	..	..	..	..	..	..	..	1	..	3	..	..	..	20
P. aeruginosa	13†	A	24	..	..	..	..	..	..	..	..	..	..	13	..	..	>12.5
	18	B	18	..	..	..	..	..	..	..	..	..	..	..	..	16	>50

* A, broth-dilution method, nitrofurantoin standard in urine; B, same with standard in broth; C, plate-dilution method in heart-infusion agar.
† Strains from current cases including those in this study; others are from other recent studies.
‡ Lowest concentration tested.
§ One strain inhibited by 22.5 mg./100 ml.

100 ml. All but 5 of 41 strains of A. aerogenes were inhibited by 12.5 mg. or less per 100 ml. (range, <2.5 to 22.5). The large group of Proteus species is of interest because of the discrepancies in the values given in previous reports † and because of the emphasis in some reports on the particular usefulness of this agent in Proteus infections. Of the 111 strains tested by the plate-dilution method, none were susceptible to 5 mg. per 100 ml.; 58 were inhibited by 10 mg.; 45 more were inhibited by 20 mg. per 100 ml., and 8 grew freely in the latter concentration after 24 hours of incubation. Only 40 of these 111 strains were inhibited by 10 mg. per 100 ml. after 48 hours. The strains of P. morgani appeared to be the most uniformly susceptible, all being inhibited by 10 mg. at 24 hours. P. mirabilis, the commonest species encountered in this hospital, and P. rettgeri both showed greater proportions of more resistant strains, and P. vulgaris was intermediate in this respect. Thus, the most sensitive strains of Proteus were less susceptible to nitrofurantoin than the majority of strains of A. aerogenes. All the strains of Pseudomonas were resistant to nitrofurantoin and grew well in the presence of the highest concentration tested, namely, 50 mg. per 100 ml. in broth at pH 7.0. The few strains of Enterococcus, viridans Streptococcus, and Staphylococcus that were tested were all sensitive.

TABLE 4.—*Results of Tests for Sensitivity to Nitrofurantoin Done on Organisms of Same Species Isolated Before and After Treatment with the Agent Was Started*

Case	Species	Minimum Inhibiting Concentration, Mg./100 Ml.		Maximum Concentration Observed in Urine During Treatment
		Isolated Before Treatment Begun	Isolated After Start of Therapy	
2	A. aerogenes	5	7.5	12.5
7	Enterococcus	2.5	1.0	25
9	E. coli	2.5	1.0	25
10	A. aerogenes	10	10	5
11	Proteus	>25	25	25
12	A aerogenes	15	25, 20, 10*	>25
18	A aerogenes	6.3	20	< 0.5
20	E. coli	1.6	0.8	3.2
21	E. coli	3.2	3.2	< 1
28	P. aeruginosa	>25	>25	6.3
29	Proteus	>25	12.5, >25*	25
36	E. coli	3.2	3.2	....
37	Proteus	>25	>25	....
39	E. coli	3.2	3.2	....
40	A. aerogenes	12.5	25	....

* Consecutive isolations.

In 15 patients there was an opportunity to test strains of the same species isolated before and after therapy was started. The results are shown in Table 4. In only two instances (Cases 18 and 40) strains of A. aerogenes isolated before and after the institution of treatment showed a twofold or greater increase in minimum inhibiting concentration, as shown in simultaneous tests. No significant changes in sensitivity in relation to treatment occurred in any of the other organisms tested, some of the later strains appearing to be more sensitive than the original pretreatment isolates.

CONCENTRATIONS OF NITROFURANTOIN IN URINE

Random specimens of urine were obtained from patients during treatment; these were Seitz-filtered, set up in twofold dilutions with broth, and incubated with a standard inoculum of the McLeod strain of E. coli; in some instances these urines were also set up with the pathogen originally isolated from the same patient. In 15 of 31 urines so tested a degree of antibacterial activity equivalent to that in a standard urine solution containing 12.5 mg. per 100 ml. of nitrofurantoin at pH 7.0 was observed; in the remainder, lesser degrees of activity were demonstrated. The standard solution of the drug in urine was tested concurrently in each instance and yielded reproducible end-points with the standard test strain of E. coli.

An attempt was also made to define the levels of nitrofurantoin activity in the urine somewhat more clearly. A normal man weighing 80 kg. was given maximum clinical doses (200 mg. four times daily, or 10 mg. per kilogram per day), and urine specimens were collected at appropriate intervals between doses and after the last dose. Each specimen was tested in 10-part arithmetic dilutions with broth as diluent, concurrently with known standard solutions of nitrofurantoin in urine and in broth, and with three test organisms, namely, a strain of E. coli and two of A. aerogenes, which had been preselected to permit the best estimation of activity. The levels in the specimens of urine were then calculated by comparisons with the standard solution for each organism in broth and in urine and at incubation periods ranging from 13 to 110 hours.

† References 1, 2, 4, 12, 24, and 25.

Although the method provided end-points that were easily read and reproducible, the estimated levels obtained for any one specimen varied with the standard reference solution, the test organism, and the length of incubation after which the tests were read. Table 5 lists the range of concentrations for each specimen as estimated by these various methods.

The results indicated a precision no greater than might be obtained by the more conventional twofold dilution methods. Nevertheless, it will be seen that levels in the range of 25 to 50 mg. per 100 cc. were obtained for four to six hours after a maximal clinical dose but that eight hours after the last dose the levels were low. It is of some interest that the estimated levels of antibacterial effect may at times exceed the apparent in vitro solubility of nitrofurantoin in urine at the pH in question as predicted from solubility curves in the same medium. The somewhat lower levels observed after the fasting dose may be related to the more dilute urine being elaborated at the time. The urine levels estimated on the basis of antibacterial effect are comparable to those reported by the spectrophotometric method.‡

‡ References 4 and 24.

Blood Levels

Many specimens of serum and citrated plasma were obtained before and at appropriate intervals after 200 mg. doses in the same subject. Single specimens of plasma were also obtained from patients on the usual therapeutic doses used for infections before and one hour after some of the doses. These specimens were set up in twofold tube dilutions and incubated with a standard inoculum of a strain of E. coli McLeod that was inhibited by 0.8 mg. per 100 ml. of nitrofurantoin at 24 hours incubation. The specimens were also tested in the same manner after heating at 56 C for 30 min. to destroy complement.

Table 5.—*Concentrations of Nitrofurantoin in Urine*

	Characteristics of Urine Sample					Range of Antibacterial Activity as Determined by Different Methods and Compared with That of a Standard Solution of Nitrofurantoin in Urine, Mg./100 Ml.	
Experiment*	Interval After Previous Dose, Hr.	Volume, Ml.	Specific Gravity	pH	Predicted Solubility in Vitro, Mg./100 Ml.	Minimum	Maximum
I.....	3-5	60	1.025	6.0	29	25	>50
	0-1	60	1.020	5.5	26	50	>50
	1-2	65	1.026	6.0	29	25	>50
	2-3	55	1.025	6.0	29	20	48
	3-4	50	1.023	5.5	26	25	>50
	4-6	95	1.025	5.5	26	17.5	35
	6-8	90	1.023	5.5	26	8	20
	8-10	55	1.028	5.5	26	0	1.6
	10-14	180	1.025	5.0	24	0	0
II.....	0-9	400	1.023	5.5	26	17.5	35
	0-1	70	1.015	6.0	29	17.5	30
	1-2	50	1.013	6.0	29	15	27.5
	2-3	50	1.023	6.5	42	25	45
	3-4	35	1.023	6.0	29	17.5	35

* Experiment I: Subject (W.A.R., man, 80 kg.) received 200 mg. doses every six hours for eight doses; first urine was collected after the seventh dose, and all others after the last dose. Experiment II: Same subject five days later took a 200 mg. dose with a meal at night after voiding and collected the overnight urine; he then took a second dose of 200 mg. fasting and collected the remaining specimens of urine after that dose.

In no instance was there observed any increase in the antibacterial effect of the serum or plasma in the specimens obtained after the administration of nitrofurantoin as compared with the pretreatment specimens.

Effect of pH and Size of Inoculum

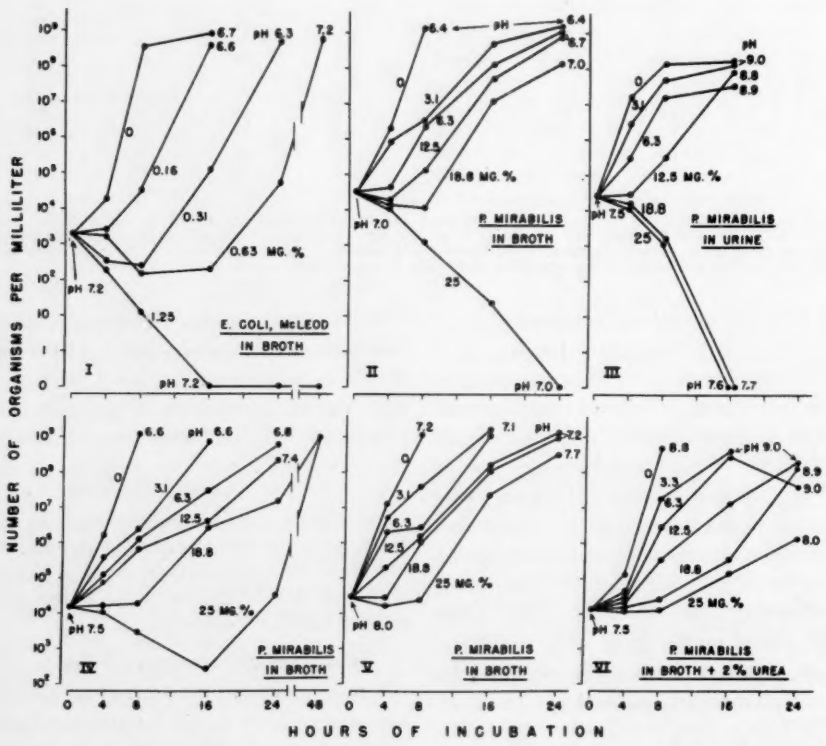
Preliminary observations were made on the size of inoculum on the end-points in the tube-dilution sensitivity test. The McLeod strain of E. coli was used in twofold broth dilutions of a standard broth solution of nitrofurantoin.

The results are shown in Table 6. Within the ranges shown, the activity of nitrofurantoin was greatest at pH 5.4 and was markedly inhibited at pH 8.1; there was also a pro-

TABLE 6.—*Effect of pH of Medium and Size of Inoculum on Inhibition of E. Coli by Nitrofurantoin* *

pH	Inoculum, Organisms/Ml.†	Method‡	Concentration of Nitrofurantoin, Mg./100 Ml.§								
			25	12.5	6.3	3.1	1.6	0.8	0.4	0.2	0.1
5.4	2,500,000	A	....	....	....	.....	.....	.....	±	++	+++
...	.....	B	....	....	....	.....	.....	.....	.....	++++	++++
5.9	2,500,000	A	....	....	....	.....	.....	.....	++	+++	++++
...	.....	B	....	....	....	.....	.....	.....	++++	++++	++++
6.4	2,500,000	A	....	....	....	.....	.....	.....	+++	++++	++++
...	.....	B	....	....	....	.....	.....	.....	++++	++++	.....
7.0	2,500,000	A	....	....	....	.....	.....	.....	+++	++++	++++
...	.....	B	....	....	....	.....	.....	±	++++	++++	.....
8.1	2,500,000	A	±	+	+	+	+++	+++	+++	+++	+++
...	.....	B	++	++	++	+++	+++	+++	+++	++++	++++
7.0	250,000	A	....	....	....	.....	.....	++++	++++	++++	++++
...	.....	B	....	....	....	.....	.....	++++	++++	++++	.....
7.0	2,500	A	....	....	....	.....	.....	.....	++	++++	++++
...	.....	B	....	....	....	.....	.....	.....	++++	++++	.....
7.0	25	A	....	....	....	.....	.....	.....	.....	++++	++++
...	.....	B	....	....	....	.....	.....	.....	+++	++++	.....

* The experiments above and below the line were done on different days.
† Made by 10-fold dilutions in broth from a 24-hour broth culture of E. coli, McLeod.
‡ A, visible growth in broth after 24 hours; B, growth after subculture of A to blood agar plate.
§ Growth is estimated on a scale 0 to ++++, the latter representing full growth in drug-free medium.



Growth of E. coli and P. mirabilis in various concentrations of nitrofurantoin.

gressive decrease in the minimum concentration of the drug required to inhibit the strain of E. coli at pH 7.0 as the size of the inoculum was decreased.

Growth Curves

Further observations on the mode of action of nitrofurantoin, and on the effect of pH were made by means of growth curves. The Figure shows the curves of the bacterial counts at several points in the course of incubation at 37 C and in selected concentrations of nitrofurantoin for a strain of E. coli in broth and for a strain of P. mirabilis in urine and in broth at various levels of pH. Determinations of pH were made at the time of each count, but, since significant changes, in general, were noted only after nearly full growth had been attained, only the initial and final pH levels are shown. Hydrogen ion concentration was measured potentiometrically (Beckman pH meter); no attempt was made to exclude air from the urine.

The curves of the growth of the McLeod strain of E. coli in broth are given in Panel I of the figure. At a starting pH of 7.2 and with an inoculum of 3000 organisms per milliliter a progressive bactericidal action occurred in a concentration of 1.25 mg. per 100 ml. of nitrofurantoin, with complete killing at 16 hours. A diminishing bacteriostatic action was noted with progressively smaller concentrations of the agent. No significant change in pH was observed in the medium until virtually full growth was achieved.

Panels II and V show growth curves for a strain of P. mirabilis in broth without added glucose, all done simultaneously but starting at pH 7.0 and 8.0, respectively. This strain had been isolated prior to treatment from one of the patients classified as a bacteriologic failure. As may be seen, at the lower starting pH (Panel II) there was complete killing by 25 mg. per 100 ml. after 24 hours and a significant degree of bacteriostasis up to 8 hours in a concentration of 18.8 mg. per 100 ml. At the more alkaline starting pH, as shown in Panel V, there was a significantly greater amount of growth at eight hours in the culture containing 18.8 mg. per 100 ml. and no progressive killing but only bacteriostasis up to eight hours at 25 mg. per 100 ml. The changes in pH during incubation were in the direction of acidity and occurred only in association with good growth.

Panel IV shows the growth curves for the same strain of P. mirabilis in broth, at an intermediate starting pH, and it is apparent that the curves here range between those shown in Panels II and V. These curves were run concurrently with those of Table 6, which shows the effect of adding 2 gm. of urea per 100 ml. to the broth used. At approximately the same starting pH, there was no very striking difference between the curves in Panels IV and VI except for a somewhat greater and more prolonged bacteriostatic action at 25 mg. per 100 ml. in the broth without the urea. This difference was not related to any significant change in pH in either system. Although in the broth containing urea the changes in pH were in the direction of alkalinity, these changes were observed only after progressive growth has been initiated and after about 100-fold multiplication had occurred. There was no apparent difference in the subsequent slope of the curves that might be attributed to the pH change.

In Panel III are given the curves for the same strain of P. mirabilis in urine, also starting at pH 7.5. Complete killing was noted at 16 hours with both 25 and 18.8 mg. of drug per 100 ml. of medium, and similar changes in pH in the alkaline direction associated with progressive growth were noted in the smaller concentrations.

COMMENT

In Table 7 are summarized the published reports on the effectiveness of nitrofurantoin in urinary tract infections, with the results of the present study included for comparison. A favorable clinical result is here taken to mean any improvement in pyuria or other signs or symptoms of infection during treatment, with no account taken of relapses. On the other hand, favorable bacteriological results are defined more strictly for the purpose of this Table; a favorable result here denotes the clearing of the infecting organisms from the urine on treatment, without reappearance in

TABLE 7.—*Summary of Clinical and Bacteriological Results of the Use of Nitrofurantoin in Urinary Tract Infections Reported in the Literature*

Authors & Reference	Cases, No.	Type of Case*	Good Clinical Results, %			Good Bacteriological Results, %			Proteus		Comments
			Acute or Uncomplicated	Chronic or Complicated	Not Described	Acute or Uncomplicated	Chronic or Complicated	Not Described	Strains, No.	Cleared, No.	
Mintzer [1]	31	All	..	..	..	..	..	61	3	3	Majority chronic or complicated; no bacteriological follow-up
Norfleet [2]	29	Acute	97	..	..	69	..	..	5	3	Chronic cases include 13 of prostatitis & 6 of cystitis; no bacteriological follow-up
	19	Chronic	..	84	..	..	5	..	..	..	
Schatten [3]	10	Acute	100	..	..	80	..	..	11	7	Follow-up: in chronic cases, 3 completely cleared, 8 initial strains replaced by new ones
	26	Chronic	..	62	..	..	12	..	..	..	
Carroll & Brennan [4]	79	All	..	..	..	..	..	67	10	9	Mostly chronic; no clinical data or bacteriologic follow-up
Hasen & Moore [5]	23	Acute	96	..	..	74	..	..	12	7	Favorable results at end of therapy; recurrence of sensitive strains & appearance of new ones after therapy were noted
	77	Chronic or complicated	..	78	..	..	21	..	..	..	
Friedgood & Ripstein [6]	290	All	148	142	..	73	49	57	218	130	Cures in 71 of 98 acute and in 59 of 120 chronic; Proteus infections; 6 with septicemia, 5 responded well
Trafton [7]	13	Acute & postop.	92	..	..	62	..	..	10	6	Follow-up for 3 mo.; 61% of chronic cases showed at least temporary bacteriologic clearing; 9 of 10 Proteus strains cleared temporarily
	36	Chronic	..	83	..	..	3	..	..	..	
Abrams & Prophete [8]	4	Acute	100	..	..	100	..	..	7	6	Mostly cystitis & prostatitis; no bacteriological follow-up; pseudomonas not cleared in 2 and replaced original organisms in 3 others
	17	Chronic	..	59	..	..	87	..	..	..	
Johnson & Marshall [9]	18	No anatomic abnormality	72	..	..	61	..	..	13	7	All children; those without abnormalities were chronic with 4 recurrences after favorable bacteriological response
	11	With abnormality	..	55	..	..	9	..	..	..	
Kaplan & Hobgood [10]	31	Acute	..	..	..	78	..	..	2	0	No bacteriologic follow-up; Proteus infections were mixed with S. fecalis
	19	Chronic	..	58	..	..	32	..	..	..	
Draper [11]	46	Chronic	..	..	..	..	35	..	8	8	All postprostatectomy & ambulatory; only 3 of 32 had negative cultures 2 wk. after therapy
Carroll [12]	121	All	..	..	67	..	..	..	..	..	No clinical or bacteriological details
Ford & Maluf [13]	8	Chronic	..	..	..	..	13	..	1	0	Primarily study of renal & hepatic function
Haex & Voorspuij [14]	8	Acute	..	..	..	100	..	..	3	3	76% of infections other than those due to Pseudomonas were controlled; no follow-up
	16	Chronic	..	..	..	..	50	..	..	..	
Jensen [15]	6	Acute	100	..	..	..	..	..	..	..	Effect on pyuria evaluated; no follow-up of bacteriology; almost all strains were sensitive
	14	Chronic	..	40	..	..	..	..	..	..	
Walsbren & Crowley [16]	60	All	..	..	45	..	..	20-33	9	8	33 strains eradicated; 13 were not, and 25 new strains, including 6 of Proteus, appeared during or immediately after therapy
Present study	12	Uncomplicated	92	..	..	75	..	..	11	3	Better and more lasting bacteriologic results in uncomplicated cases; see previous tables
	18	Complicated	..	64	..	..	36	..	..	..	

* Most of "acute" cases were uncomplicated; most of chronic cases had recognized complications (abnormalities).

the follow-up period, when follow-up data were available. However, cases have not been excluded for lack of follow-up. The appearance of new infecting organisms in the course of treatment has not been regarded as a bacteriologic failure in this study, and probably in all other studies; accordingly, only the performance with respect to the initial infecting organisms is considered in this Table.

In all studies, including this one, it is apparent that most cases of acute or uncomplicated infections respond favorably, both clinically and bacteriologically. However, the self-limited nature of such infections must be taken into account. Chronic and complicated infections also show some clinical improvement on treatment in most instances. The bacteriologic effectiveness reported in such cases, however, is less consistent, and the more favorable reports appear to be those in which no follow-up data are available.

The true usefulness of any antimicrobial agent in urinary tract infections is difficult to evaluate because of the primary importance of complicating factors in determining the results. The presence of complications, rather than chronicity, was, therefore, selected as a basis for analysis in the present study. Clearing of an infecting organism from the urine in the course of treatment only indicates the effectiveness of the agent in the concentration achieved in the urine against the organism in question, and it need not necessarily bear any relation to the effect upon the infectious process. An agent which does not achieve effective levels in the blood or tissue fluids may not yield optimal effects. The inconsistent results here obtained in cases of acute pyelonephritis, albeit many of them were complicated, and particularly the occurrence of bacteremia in two cases during the course of treatment with the agent, support this view. However, no final proof is at hand that a "urinary antiseptic" is necessarily any less "curative" than antimicrobial agents producing effective blood levels. Complications remain the deciding factor in most instances. These and other aspects of antimicrobial therapy of urinary tract infections have been reviewed recently.[21]

The ineffectiveness of nitrofurantoin in Pseudomonas infections and the frequent emergence of this organism as a new pathogen in the course of treatment of complicated infections has been noted by other workers and is further documented in this study. E. coli, the commonest urinary tract pathogen, is the organism most consistently eliminated; the bactericidal action of the drug against this species at relatively low drug concentrations may be the determining factor in this effect.

Many papers on nitrofurantoin have placed particular emphasis on its usefulness in Proteus infections (see Table 7). In the present study none of eight infections with Proteus in which follow-up data were availble was permanently cleared of this organism. The persistence of organisms in reduced numbers in the urine during the course of treatment, and their reappearance in the large numbers characteristic of active infection after treatment is stopped, was noted in three patients with Proteus infections and is evidence that the bacteriostatic action of nitrofurantoin fails to achieve permanent clearing of these infections. In addition, the alkaline pH of the urine in established Proteus infection may play a significant role in further lessening the effectiveness of nitrofurantoin.

As to toxic manifestations, the gastrointestinal disturbances seem to be largely, though not invariably,[4] a function of dosage, and they generally represent no serious problem. Others have described cutaneous and febrile reactions suggesting the development of hypersensitivity to the drug.§ No such reactions were noted in this study. No evidence of renal toxicity in the form of hematuria, albuminuria, crystalluria, or azotemia (not ascribable to the underlying renal lesion) was observed in the course of this study, and none has been reported. Renal and hepatic functions were studied by others, and no impairment due to nitrofurantoin was found. The two instances of arrested erythropoiesis reported here were probably coincidental, since there were other known factors

§ References 4, 5, 7, 11, and 15.

to account for them. The only observation suggesting any bone marrow effect is the report of a single case of simple leucopenia.[5] Nevertheless, another organic compound of related structure, diphenylhydantoin, has been implicated as a cause of bone marrow depression, and so the possibility of this complication resulting from nitrofurantoin must be kept in mind. The depression of spermatogenesis by massive doses of the agent in experimental animals is mentioned,[5] with no evidence for such an effect in man on therapeutic doses in limited morphologic studies.‖ There remains in this also the suggestion that the agent may have some action on cells undergoing rapid cell division, but this effect is unlikely during therapy of patients, owing to the low concentrations achieved in blood and tissue fluids.

The values for sensitivity of urinary pathogens to nitrofurantoin here reported correspond rather closely with those found by others. Strains of E. coli were all sensitive to relatively low concentrations, whereas those of A. aerogenes and of various Proteus species were more variable and, in general, less sensitive and those of Pseudomonas were all highly resistant. The few strains of streptococci and staphylococci tested were sensitive to low concentrations. The results of tests for sensitivity of strains of Proteus as reported by others are listed in Table 8 and show considerable variation, as did the strains in the present study, listed in Table 3. Among the species of Proteus studied here the commonest one, P. mirabilis, showed a high proportion of more resistant strains. Increasing resistance of organisms during the course of treatment did not seem to constitute a significant problem in the present cases but may possibly be a factor in some cases of A. aerogenes infections.

Data on the levels of nitrofurantoin in urine, as determined spectrophotometrically, have been reported.¶ Beutner and co-workers [24] reported maximum levels of 37 to 46 mg. per 100 ml. in three normal subjects and of 20 to 30 mg. per 100 ml. in three subjects with urinary infections. Data are presented here which indicate that levels of antibacterial activity in the urine may be obtained which are comparable to those estimated by the ultraviolet absorption technique. By the bacteriological method used, which is admittedly crude, it appears that the levels obtained in urine may actually exceed the predicted solubility of nitrofurantoin in urine, as has been previously claimed.[19]

Carroll and co-workers # measured blood levels of nitrofurantoin spectrophotometrically and noted average levels of 0.22 mg. per 100 ml. or less on the usual dosage regimens. Their conclusion that clinically

TABLE 8.—*Susceptibility of Strains of Proteus as Reported by Others*

Authors	Strains, No.	Method of Testing	Results
Mintzer [1]	20	Tube-dilution	All inhibited by 6.27 (±0.57) mg./100 cc.
Norfleet [2]	4	Tube-dilution*	All resistant to 30 mg./100 cc.
Carroll & Brennan [4]	28	Tube-dilution	Min. inhibiting conc. (M.I.C.) 7.5 mg./100 cc., 10 strains; 15 mg./100 cc., 17 strains
Beutner [24]	9	Tube-dilution	M.I.C. 1.87 mg./100 cc., 1; 7.5 mg./100 cc., 1; 15 mg./100 cc., 3; 30 mg./100 cc., 2; not inhibited by 30 mg./100 cc., 2
Carroll [12]	94	10 mg. disc on agar	84 of 89 strains "sensitive"
Felton & Kemp [25]	12	10 mg. disc on agar	11 of 12 strains "sensitive"
Jensen [15]	9	Plate-dilution	Av. M.I.C. 4.16 mg./100 cc. (range 1.87-7.50)
Present study	131	(See Table 3)	.....

* With polyethylene glycol 300.

‖ References 4, 16, and 26.

¶ References 12 and 24.

References 4 and 12.

useful blood levels are obtainable is open to question, in view of the values generally reported for the sensitivity of almost all organisms, including highly sensitive strains of E. coli, which require greater concentrations than those reported in blood in order to inhibit bacterial multiplication. The data here presented fail to give any evidence of antibacterial activity in the blood attributable to administration of nitrofurantoin.

The growth curves presented demonstrate that nitrofurantoin is bacteriostatic and may be bactericidal for many organisms at higher concentrations and under suitable conditions. There is a definite impairment of antibacterial effectiveness against E. coli and P. mirabilis at alkaline pH. Proteus was selected for particular study here because of its inherent property of rendering alkaline solutions containing urea and because of the special claims made for the usefulness of nitrofurantoin in Proteus infections. It appears that a significant degree of alkalinization occurs only after progressive growth is initiated, and therefore the bacteriostatic action of the agent at a lower initial pH should prevent the occurrence of the adverse effect of urea-splitting. However, in an established Proteus infection, when the urine is already alkaline, this unfavorable influence may be important. Moreover, some degree of bacteriostasis is still exerted at the higher pH, and this, if continued and adequate, may, in turn, result in lowering the pH and improving the effect. It is further suggested that acidifying agents such as ammonium chloride might enhance the usefulness of nitrofurantoin against Proteus infections. Also, the failure to demonstrate the development of resistant variants in vitro,* if it can be confirmed, suggests that nitrofurantoin may be useful as a suppressive agent for prolonged administration in chronic urinary tract infections, but evidence to support its effectiveness when used in this manner is still lacking.

SUMMARY AND CONCLUSIONS

The clinical and bacteriologic effects of nitrofurantoin in the treatment of urinary tract infections were studied in 39 patients, 1 of whom was treated during two episodes. The results are compared with those reported by others.

Favorable clinical effects were obtained in the great majority of acute and uncomplicated infections but in a much smaller proportion of chronic cases with underlying complicating conditions in the urinary tract.

The proportion of favorable bacteriological effects varied considerably, depending on the causative organisms and on the proportion of cases in which follow-up studies were made. The most favorable bacteriological results were obtained in infections with E. coli and in the small number of cases with Gram-positive cocci; infections with Pseudomonas were not affected, and new strains of this organism frequently appeared as new invaders; the results in Aerobacter infections were intermediate. Proteus strains were temporarily inhibited, but follow-up studies indicated that they were usually not cleared and that they sometimes appeared as new invaders during or promptly after treatment.

Toxic effects attributable in nitrofurantoin were minor and consisted mostly of nausea and vomiting that was often related to the dose used. Sensitivity reactions were not encountered but have been reported by others.

Levels of nitrofurantoin in blood and urine as determined by antibacterial action indicated that effective concentrations are excreted in the urine but that useful levels are not attained in the blood on oral therapy. The levels observed by this method are comparable with those obtained by others using a spectrophotometric method.

In vitro studies, including growth curves, indicate that the antibacterial action of nitrofurantoin is considerably depressed at the highly alkaline pH attainable in urine or when there is an excessive concentration of organisms. These studies also confirm the primary bacteriostatic action of the drug, with a bactericidal effect on more susceptible strains demonstrable at higher concentrations.

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The Use of Myleran in the Treatment of Chronic Myelocytic Leukemia

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A sulfonic acid ester, Myleran (1,4-bis [methylsulfonyloxy]butane) (Fig. 1), synthesized by Timmis,[1] was introduced by Galton [2] for the treatment of chronic myelocytic leukemia. This agent appears to be so promising that it seemed worth while to publish a full account of our own experience

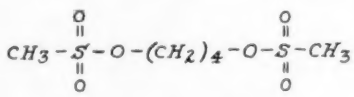

Fig. 1.—The structural formula of Myleran (1, 4-bis[methylsulfonyloxy]butane).

with it. Preliminary findings in some of our cases have been reported already.[3] In addition to the latter and the 19 patients treated by Galton,[2] the results of treatment of only 40 other cases have been reported until now.*

MATERIAL

Since November, 1952, we have used Myleran in the treatment of 16 consecutive cases of chronic myelocytic leukemia (Table 1). Eleven had received no previous therapy; five cases had been treated earlier with x-rays, nitrogen mustard, triethylenemelamine, or radioactive phosphorus. The interval from the apparent onset of leukemia to the start of Myleran therapy ranged from 1 month to 56 months; in seven cases it was 1 year or longer. For the 11 patients whose first treatment was with Myleran, this interval ranged from 1 to 13 months, and in 7 it was 6 months or longer. The period of observation since Myleran was first prescribed is more than two years in six cases and more than one year in three other cases.

Status of Patients at the Start of Myleran Therapy (Table 1).—In addition to the characteristic changes in the blood (and marrow, when this was examined), in 15 of 16 patients there was splenic enlargement. In four cases this organ extended from 1 to 4 cm. below the left costal margin in the midclavicular line; in eight cases it was of greater size, measuring 12 to 25 cm. beyond the same landmark. The remainder were intermediate in size. Hepatomegaly was present in 13 cases, including the 1 without a palpably enlarged spleen. Substantial anemia, that is, a volume of packed red cells of less than 39 ml. per 100 ml., was present in nine cases. In the remainder the volume of packed red cells ranged from 39.5 to 53.5 ml. per 100 ml. Four of the patients without anemia had not been treated previously. One other had been transfused a few weeks earlier, and two had recently been treated with triethylene melamine.

Mode of Treatment.—Myleran was administered to 16 patients for a total of 40 courses of treatment. To date, 16 first courses of treatment, as well as 10 second, 6 third, 5 fourth, 1 fifth, and 1 sixth course have been completed (Table 2). The results of these are described below.

In the main, oral doses of 4 to 6 mg. daily were prescribed, to be taken before the morning meal. Except for a single patient given 24 mg. daily for six days, the average daily dose for the completed courses of treatment in the whole series was 4.5 mg.; the duration of therapy ranged from 21 to 269 days. For the most part, patients received treatment for from 42 to 71 days. The total dose administered per course ranged from 84 to 849 mg.

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* References 4-6.

TABLE 1.—*Cases Treated with Myleran*

Case No. and Initials	Sex	Previous Therapy	At Initiation of Myleran Therapy: Age, Yr.	At Initiation of Myleran Therapy: Duration of Disease, Mo.*	Status After Myleran Therapy	Duration of Disease, Mo.†: Since Beginning Myleran Therapy	Duration of Disease, Mo.†: Total
1. E. F.	F	None	46	3	Symptom-free, blood normal, spleen tip palpable	25	28
2. M. J.	F	One transfusion	57	1	Symptom-free, WBC 15,000, VPRC normal, spleen tip palpable	10	11
3. J. R.	M	None	38	1	Symptom-free, WBC 10,300, VPRC 43.5, spleen not felt	8	9
4. G. P.	F	None	38	12	Symptom-free, WBC 4,400, Hb. 12.0 gm. per 100 cc.	6	18
5. C. B.	M	May, 1951, x-ray to spleen, 1100 r	64	30	Symptom-free, WBC 16,000, VPRC 46, spleen not felt	22	52
6. A. T.	F	None	65	10	Feels well, WBC 130,000, VPRC 56, spleen large	25‡	35
7. D. R.	M	X-ray	69	16§	Died, see Fig. 5	14	30
8. J. S.	M	Nitrogen mustard in 1950, 1951; urethan, 1950; P^{32}, 1951-1953	67	56	Died, see text	2	58
9. G. W.	F	None	65	8	Symptom-free, WBC 9,400, VPRC 34, spleen at costal margin	5	13
10. R. B.	M	None	58	13	Symptom-free, WBC 75,000, VPRC 58, spleen large	7	20
11. E. B.	F	Four transfusions, 1952; TEM 1952	66	18	Died, see text	18	36
12. B. K.	F	None	61	4	Symptom-free, WBC 38,000, VPRC 42, spleen not felt	29	33
13. M. W. G.	F	None	23	6	Died, see text	26	32
14. V. H.	M	TEM, 1952	50	12	Symptom-free, WBC 21,250, VPRC 45, spleen moderately enlarged	27	39
15. C. A.	F	None	10	8	Symptom-free, WBC 10,800, Hb. 12.4 gm. per 100 cc., spleen at costal margin	26	34
16. E. C.	F	None	58	10	Symptom-free, WBC 11,500, VPRC 44	5	15

* From onset of symptoms, or diagnosis, whichever was earlier.
† Until death, or April 15, 1955, if living.
‡ See Table 2. Received x-ray therapy after second course of Myleran; now receiving third course of Myleran.
§ This patient had polycythemia four and one-half years previously.

Repeated courses of therapy required doses of the same magnitude as the initial course, or slightly less, except for one patient (Table 2, V. H., Case 14) in whom the second and third courses required nearly three times the original dose to reduce the leucocyte count below 10,000 per cubic millimeter.

When calculated according to the patient's weight, the average daily dose per course ranged from 46γ to 109γ per kilogram of body weight, except for a child of 10 years, in whom it was 223γ per kilogram, and in the patient given 24 mg. per day, in whom it was 451γ per kilogram.

Patients were ambulant while receiving the drug. They were examined at one- to three-week intervals. Therapy was usually continued until the desired result, as described below, was obtained. In two cases thrombocytopenia, without purpura, prompted early withdrawal of the drug. In four patients treatment was interrupted prematurely to avoid the risk of overdosage. After therapy had been stopped, follow-up examinations were made at one- to three-month intervals. Maintenance therapy was not attempted. Subsequent courses of therapy were begun, as will be described later, when the signs of relapse were thought to warrant it.

RESULTS OF TREATMENT

A decrease in the leucocyte count and other favorable changes were observed in all cases and in all courses of treatment. In patients with only partial improvement after the initial therapy, a subsequent course gave better results.

Subjective Changes.—Often within the first two weeks of treatment the patients noted a sense of well-being which they had previously lacked, return of appetite, and improvement in endurance. The undernourished patients soon noted a definite gain in weight. These changes first made their appearance prior to any significant relief of the anemia or decrease in splenomegaly and corresponded with the early reduction in the leucocyte count. Thereafter, except for three patients (Table 2; C. B., D. R., M. W. G.; Cases 5, 7, 13), all remained symptom-free despite evidence of relapse which warranted

TABLE 2.—*Results of Myleran Therapy*

Case No.	Courses of Therapy No.	Days Since Previous Therapy	Av. Dose, Mg./Day	Av. Dose, γ/Kg./Day	No. Days in Course of Treatment	Total Dose per Course	WBC/Cu. Mm.		VPRC		Platelets		Spleen Size, Cm.	
							Initial *	Final *	Initial	Final	Initial	Final	Initial	Final
1. E. F.	1	...	3.9	73	71	280	146,250	10,000	35.0	42.0	1,900,000	>200,000	1 †	0
	2	361	4.0	75	70	280	45,100	8,300	40.5	41.0	Excessive	200,000	0	0
2. M. J.	1	?14	4.7	71	69	326	98,750	10,250	45.5 ‡	44.0	526,000	>166,000	4	1 †
3. J. R.	1	...	4.0	53	48	192	61,350	10,300	52.0	43.5 §	576,000	>225,000	0	0
4. G. P.	1	...	4.0	90	63	252	210,250	11,600	28.0	36.0 §	440,000	? ‖	6	1 †
	2	14	4.0	90	21	84	?	4,400	?	36.0 §	?	?	1 †	0
5. C. B.	1	780	4.0	46	43	172	95,000	18,000	46.0	45.0	440,000	?	1	?
	2	270	4.0	46	38	152	41,500	25,000	?	53.0	?	?	?	?
	3	45	4.5	51	63	286	62,000	10,800	50.0	49.0	860,000	?	6	?
	4	110	6.0	79	43	248	34,500	14,350	53.0	46.0	?	?	?	?
6. A. T.	1	...	3.0	49	269	800	153,000	21,000	41.0	44.5	116,000	94,000	25	11
	2	41	4.0	60	110	440	32,600	20,500	48.0	45.0	100,000	52,000	15	12
		167	X-ray, 500 r to spleen			...	154,000	41,000 ¶	58.0	51.0	115,000	63,000	22	17
	3	...	4.0	..	..	...	130,000	72,000	56.0	?	111,000	44,000	24	Smaller
7. D. R.	1	150	4.7	75	91	430	377,500	9,150	28.0	42.0 ‡‡	594,000	80,000	24	10 → 0
8. J. S.	1	60	4.5	76	56	252	247,750	40,000	32.0	44.0	100,000	>294,000	9	4
9. G. W.	1	...	4.8	69	132	632	234,000	9,400	30.5	34.0	258,000	>157,000	12	1 †
10. R. B.	1	...	4.0	66	66	264	99,000	23,000	53.5	63.0	330,000	80,000	17	15
	2	92	4.0	..	..	...	153,750	.....	56.0	....	>158,000	.....	20	..
11. E. B.	1	30	4.7	79	91	426	265,500	14,850	30.5	43.5	>422,000	>400,000	17	3
	2	211	5.3	80	63	336	130,000	19,995	37.0 **	39.5	Excessive	>512,000	5	3
12. B. K.	1	...	6.0	80	28	168	191,250	12,550	32.0	38.5	320,000	346,000	12	11 → 3
	2	39	3.5	52	42	146	49,750	9,000	42.0	40.0	300,000	284,000	3	2½
	3	143	3.9	57	46	180	53,750	7,800	40.5	43.0	300,000	186,000	2	0
	4	277	4.0	57	42	168	67,150	7,600	42.0	44.5	>190,000	200,000	0	0
13. M. W. G.	1	...	24.0	451	6	144	553,000	260,000	25.0	28.0	110,000	180,000	To both I.C.††	To left I.C.
	2	24	5.5	100	42	230	116,000	8,100	34.0	39.0	308,000	300,000	To left I.C.	6
	3	170	4.0	72	35	140	35,000	5,500	36.5	34.0	66,500	54,000	4	0
	4	49	5.5	103	31	170	74,800	10,900	38.5	39.0	136,000	36,000	4	0
	5	58	4.6	84	38	176	95,000	5,400	38.5	34.5	54,000	38,000	0	0
	6	92	6.0	109	16	96	157,000	40,600	35.0 §	?	13,000	16,200	7	?
14. V. H.	1	...	4.7	56	59	278	115,000	14,600	41.0	37.0	408,000	Excessive	6	3.5
	2	58	4.3	51	172	742	55,700	9,850	39.0	50.0	>220,000	>346,000	4	1
	3	183	4.7	58	175	830	94,500	14,650	43.0 ‡‡	45.5	>980,000	>992,000	6	5
	4	60	5.7	69	149	849	75,100	11,200	43.0	47.0	>760,000	513,000	10	2
15. C. A.	1	...	4.7	223	85	396	446,000	7,400	25.0	42.0 §	>1,032,000	128,000	>15	1.5
	2	246	4.0	176	38	152	58,900	7,450	39.0 §	41.0 §	264,000	214,000	4	0
	3	96	4.0	170	32	128	42,875	8,250	37.0 §	45.0 §	3?0,000	196,000	2	0
	4	95	4.0	162	29	116	41,500	10,800	41.0 §	37.0 §	309,000	180,000	2	1 †
16. E. C.	1	...	4.0	78	49	196	80,850	6,800	39.5	41.0	2,368,000	Excessive	2	?1
	2	28	3.9	75	13	50	18,500	11,500	45.0	44.0	?	358,000	?	?

* Initial and final values are those at the time a course of Myleran was begun and completed, respectively.
† Only "tip" recorded.
‡ This patient had been transfused prior to this determination.
§ Calculated from hemoglobin values, assuming MCHC 33% (cells were normochromic).
‖ ?, information missing.
¶ Lowest value attained.
‡‡ Subsequently developed pancytopenia (see Fig. 5).
** In the interval this patient bled from a peptic ulcer.
†† I.C., iliac crest.
‡‡ Episode of gastrointestinal bleeding preceded this.

retreatment in 10 cases. Of the three exceptions, purpura was the complaint in one case; in another there was constant fatigue during a period of relapse, but this was relieved by retreatment, and in the third there were transient weakness and purpura, attributable to the development of pancytopenia following treatment.

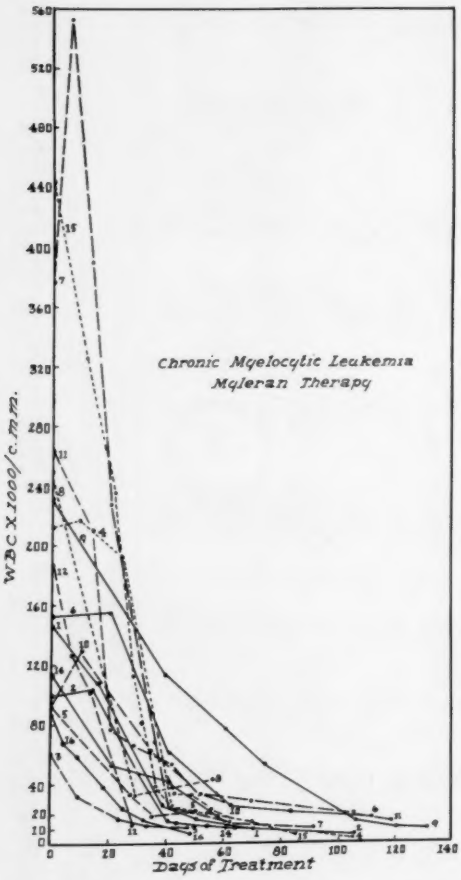

Fig. 2.—The changes in the leucocyte counts associated with Myleran therapy. The leucocyte values during the initial therapy are shown for 15 patients. The one patient who received 24 mg. of Myleran for six days as initial therapy is not included.

Leucocytes (Fig. 2).—Within the first two weeks of treatment a fall in the leucocyte count was usually noted. In occasional instances, in particular when the leucocyte count was rising rapidly to high levels prior to therapy, the count did not fall below the original value until after three weeks of treatment. The decline in the leucocyte count, for a given dose per day, described an exponential function.

The locus of successive leucocyte counts plotted on semilogarithmic graph paper, with time represented on the linear scale of the abscissa, closely approximated a straight line in most cases. The rate constant (k) for the change in the leucocyte count could be determined when such a straight line was defined by three or more points, thereby validating the application of the equation $\frac{-dW}{W} = k\ dt$ †

The maximum slope ‡ of the line indicated the maximum effect of the drug. The value of the rate constant, at maximal effect, was found to vary with the dose of Myleran administered. Calculations based on data from 13 patients § receiving 40γ to 110γ per kilogram per day during an initial course of Myleran therapy afforded an approximation of this relationship. A positive linear correlation could not be established between the rate constant and the dose. Consideration of a first order equation yielded a correlation coefficient of 0.53. The coefficient of correlation was greater when k was considered to be a sine function of the dose (Fig. 3). In that instance the coefficient was 0.84. The probability that this indicated a positive correlation was greater than 0.99, as evaluated by the t-test. It appears, therefore, that the time required for a given leucocyte count to return to normal under initial treatment was proportional to the logarithm of the initial count and was related to the daily dose of Myleran per unit body weight.

When the leucocyte count was 11,000 per cubic millimeter, or greater, at the time Myleran was stopped, it tended to rise shortly thereafter. In those cases in which

† W, leucocyte count; t, time; k, the rate constant.

‡ Maximum slope was used if the initial segment was convex.

§ Three patients received more than 110γ per kilogram per day (see Table 2). The values of k were 0.091, 0.113, and 0.148 days^{-1} at doses of 128γ, 190γ, and 451γ per kilogram per day, respectively.

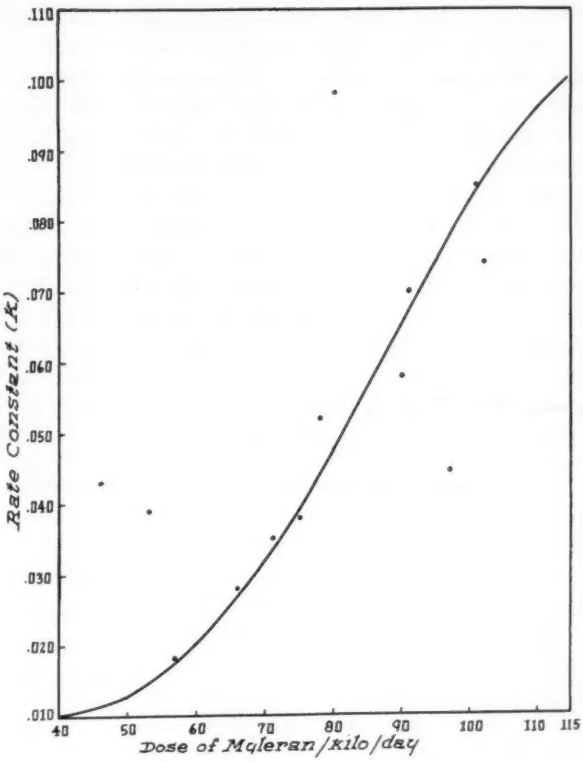

Fig. 3.—The curvilinear relationship between the dose of Myleran expressed in micrograms per kilogram per day and the rate constant (k) in days^{-1} for the daily change in the leucocyte count. Values for the initial therapy of 13 patients are shown by the points. The hypothetical curve represents $\pi/2$ radians of a sine curve.

therapy was continued until the count was less than this number, the tendency for a prompt increase to occur was definitely reduced and was reflected in a longer interval before retreatment was considered to be indicated. This will be described later. A similar phenomenon has been noted following x-ray therapy.[7]

In only 4 instances among 39 completed courses of therapy did the decline in the leucocyte count, after Myleran had been discontinued, continue to leucopenic levels. In one case (Table 2, C. A., Case 15) the leucocytes decreased from 7400 to 4050 per cubic millimeter; 48% of the latter were neutrophiles. The count returned to normal within eight weeks. Following another course of therapy in this patient there was a transient decrease to 4400 leucocytes per cubic millimeter for one week. Another patient (Table 2 D. R., Case 7) developed pancytopenia. This complication is described in detail in the discussion of the toxicity of the drug. In the third patient (Table 2, G. W., Case 9) there was a transient decrease to 4500 leucocytes per cubic millimeter.

As the leucocyte count fell, the immature granulocytes decreased in number more quickly than the neutrophiles, and they disappeared from the blood before the total leucocyte count reached 10,000 per cubic millimeter. Other authors || have reported that the decline in the number of immature granulocytes begins distinctly before there is a reduction in the mature neutrophiles.

It is of interest that, although the immature granulocytes disappeared from the blood after treatment, an increased number of basophiles, so characteristic of chronic myelocytic leukemia, persisted in four patients. One hundred twenty-five to eight hundred basophiles per cubic millimeter were found in the blood during remissions.

|| References 2, 6, and 8.

The lymphocytes were not greatly affected by Myleran. They seldom numbered more than 8000 per cubic millimeter before treatment, and, though their number regularly decreased with Myleran therapy, they rarely fell below one-seventh of this value. In contrast, the granulocytes may have been reduced to as few as one one-hundredth of their initial value during the same period.

Volume of Packed Red Cells (VPRC).—A substantial degree of anemia, which was present in nine patients prior to treatment, was completely relieved in six of them by the initial therapy and in the seventh during the second course of treatment; in the eighth because of anemia just before she was referred to us for therapy.

At the start of the second or later courses of Myleran therapy, 4 of 11 patients were anemic. The degree of anemia was much less than that present before the initial treatment, the lowest VPRC being 34 ml. per 100 ml., whereas in the anemic patients undergoing initial treatment the highest value was 35 ml. per 100 ml. In one of these four patients (Table 2, M. W. G., Case 13) anemia had not been influenced by the first course of therapy but was relieved by the second course. During both the third and the fourth courses the VPRC fell from 38.5 and 36.5 ml.

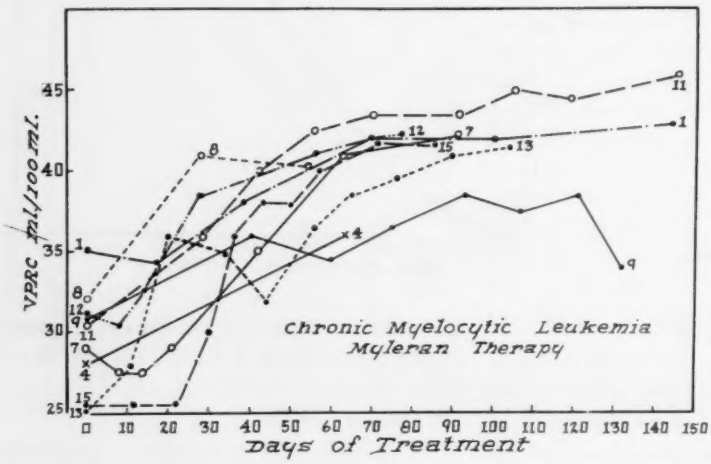

Fig. 4.—Changes in the volume of packed red cells in patients treated with Myleran. Values for nine patients with anemia prior to therapy are shown, illustrating that therapy regularly increased the VPRC.

patient there was marked improvement, while in the ninth there was only a slight increase in VPRC (Fig. 4). Transfusions have not been necessary. In the patients without anemia, there was sometimes an initial small, but temporary, decline in the VPRC coincident with the initiation of therapy.

Among the 16 patients in whom the primary course of treatment was completed, the VPRC increased in 12. The mean increment above the initial value was 30%. Two of these twelve patients were not anemic when therapy was instituted. In one other patient without anemia, when we first examined her, there was an initial fall to anemic levels and then a spontaneous return to normal. This patient had been transfused per 100 ml., respectively, to 34.5 ml. per 100 ml. It is of interest that this patient had received the highest daily dose of any of our patients, namely, 24 mg. (451γ/kg.) of Myleran per day during initial therapy. In the remaining three patients (Table 2; G. P., E. B., and C. A.; Cases 4, 11, and 15) there was no change in one and moderate and marked increases in VPRC in the other two, respectively.

Platelets.—In one-third of our cases the platelet count decreased during therapy. Since the platelet count is often greater than normal in untreated chronic myelocytic leukemia, this change usually did not produce thrombocytopenia and was not significant clinically. However, in four patients (to be

discussed in the section on toxicity) the platelet count eventually fell below 100,000 per cubic millimeter, and in two of these cutaneous purpura developed. Except in these two purpuric patients, when the platelet count decreased during therapy it increased when Myleran was stopped. As mentioned earlier, 2 of the 40 courses of treatment begun to date have been interrupted because of thrombocytopenia, to avoid purpura. On the other hand, Myleran was administered in nine courses of therapy to three patients despite initial platelet counts of 13,000 to 136,000 per cubic millimeter. Slight and temporary aggravation of the thrombocytopenia resulted, with the appearance of purpura in one patient (M. W. G., Case 13, Table 2) already mentioned above. None of our patients has had serious bleeding due to Myleran-induced thrombopenia.

Spleen.—In all of the 15 patients in whom it was enlarged the spleen was decidedly reduced in size by therapy. In two patients this organ extended to both iliac crests prior to therapy with Myleran. After treatment, in both these patients, the spleen could no longer be palpated. In five additional patients the spleen became impalpable or barely palpable after therapy.

Bone Marrow.—Repeated examination of the bone marrow was not considered necessary for the proper management of therapy, and this procedure was not performed routinely. Consequently, this aspect of the hematological changes cannot be described.

Duration of Improvement.—Therapy relieved the patients' symptoms, and almost all have continued to feel well, even though, after a period, signs developed which we interpreted as a signal for retreatment. A rising leucocyte count was the first evidence that the disease was escaping from control. In most cases therapy was not reinstituted until the count had increased to the range of 50,000 to 100,000 per cubic millimeter, although even at this point many patients were symptom-free. Only three developed anemia with the relapse, and this anemia was of modest proportion, as described earlier. An increase in the size of the spleen occurred in seven cases.

In general, the interval between courses of treatment, according to our system of management, underestimates the duration of the clinical improvement which results from treatment. The intervals between courses of treatment are given in Table 2. It can be seen that, except for instances of early retreatment because of premature interruption of the preceding course, the intervals were in the neighborhood of 100 to 361 days, with the advantage for the cases with the lower final leucocyte count following the preceding course of treatment. There were 17 instances of retreatment in which the leucocyte count was less than 11,000 per cubic millimeter at the end of the previous course. In nine of these the interval was greater than three months, including one instance in which it was one year. Among 11 instances of retreatment in which the leucocyte count was greater than 11,000 per cubic millimeter at the end of the previous course, there were only 3 in which the interval was greater than three months, the longest being nine months. The Table also illustrates that the interval between succeeding courses does not necessarily become shorter and shorter.

Resistance to Myleran.—None of our patients has failed to respond to the drug, but in two patients the susceptibility to the agent seemed to have been reduced after the first course. In none has there been a transformation to the "acute myeloblastic phase." Both of these complications have been observed, however, by Galton.[2] It has been shown that Myleran is of no value when such a transformation takes place ¶ and that 6-mercaptopurine may be useful.#

Toxicity.—There were no instances of gastrointestinal upset or anorexia such as occur with nitrogen mustard, triethylenemelamine, urethan, and x-radiation. Nor were there evidences of other undesirable effects, except on the hemopoietic system.

¶ References 2 and 6.

References 3 and 9.

There were four instances of thrombocytopenia, as mentioned earlier, in which the platelet count was reduced below 100,000 per cubic millimeter by therapy. In one (Table 2, A. T., Case 6) the platelet count was 116,000 per cubic millimeter before treatment, as compared with 94,000 per cubic millimeter afterward. This serves to illustrate the insignificant change that may occur even in the face of initial thrombocytopenia. In a third course, however, greater thrombocytopenia developed. The second patient (Table 2, M. W. G., Case 13) had received 24 mg. of Myleran daily for the first six days and after an interval of 28 days was given a second course. As a result, a total of 374 mg. was given in the first 76 days. Following this, the platelet count and other findings were normal, but thereafter the count declined so that 170 days after the end of the second course the platelets numbered 66,000 per cubic millimeter. Their number never returned to normal, although four subsequent courses of therapy were completed successfully. In the third patient (Table 2, D. R., Case 7) the thrombocytopenia was part of a pancytopenia which developed one month after therapy was stopped. This patient received 8 mg. (128γ per kilogram per day) of Myleran for a period of two weeks and was our only case of pancytopenia (Fig. 5). In the fourth case (Table

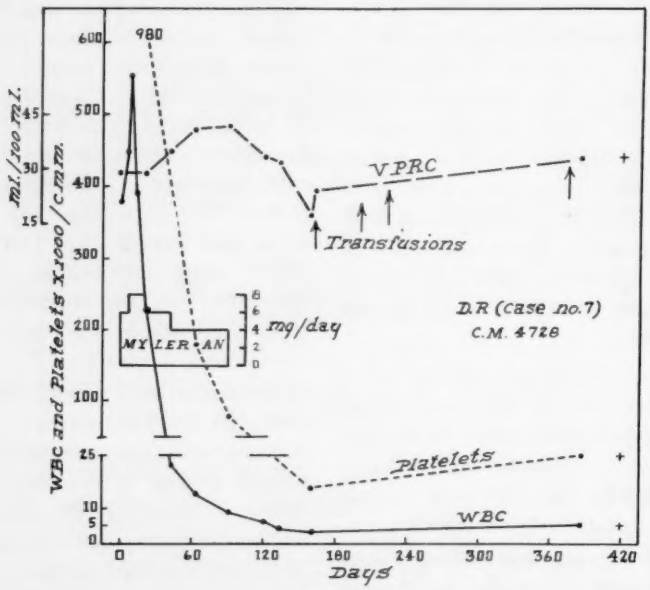

Fig. 5.—Pancytopenia following Myleran therapy (D. R., Case 7, Table 1). Man 69 years of age had received several courses of x-ray therapy, the last ending six months before Myleran was begun. In addition to leukemia, there was evidence of chronic renal disease (albuminuria, cylindruria, and blood urea nitrogen values of 33 to 42 mg. per 100 cc.). He received 430 mg. of Myleran in 91 days during two weeks of this period at a dose as high as 8 mg. per day. At the time Myleran was stopped the patient had obtained symptomatic relief and had gained from 136 to 146 lb.; the spleen had decreased in size from 24 cm. below the left costal margin to 11 cm., and later it could not be palpated at all. There was an initial spontaneous rise in VPRC, but subsequently pancytopenia developed. A sternal marrow aspiration performed at the time the pancytopenia was most marked yielded a hypocellular specimen. Another examination, seven months later, when pancytopenia was still present, yielded a cellular specimen with a myeloid-erythroid ratio of 10:1; there were 21.75% myeloblasts and reticulum cells, 7.5% promyelocytes, 14.0% myelocytes, 26.5% metamyelocytes, 8.25% segmented granulocytes, 11% lymphocytes, 2.25% plasma cells, 1.75% monocytes, and 7.0% normoblasts. Megakaryocytes were very scarce. The patient felt relatively well, in fact, better than one year earlier, prior to Myleran therapy. Four weeks later it was learned that he had suddenly become extremely ill, with nausea and vomiting and increased anemia, although the leucocyte count was unchanged. He received a number of transfusions at another hospital but died nevertheless. No autopsy was performed.

2, R. B., Case 10) there were no qualifying factors pertaining to the thrombocytopenia.

Deaths.—Four patients have died. Myleran may or may not have been implicated in two cases and definitely was not implicated in two others. The course of one of these patients is described in Figure 5. Another patient (Table 2, M. W. G., Case 13) developed thrombocytopenia after the second course of Myleran therapy had been completed. She was given four courses of Myleran subsequently and died of a cerebral hemorrhage at another hospital eight months after the last course, after having received x-ray therapy in the interim. The third patient (E. B.) underwent subtotal gastrectomy at another hospital, after her fourth massive hemorrhage from a known peptic ulcer of the stomach; she did not have thrombocytopenia. She died two months after the operation, under obscure circumstances, never having returned to our observation. The fourth patient (J. S.) died at another hospital after a three weeks' hospitalization there. The circumstances surrounding his death are also obscure, but in this case postmortem specimens of the liver, spleen, and bone marrow were sent to us for review, although a formal complete autopsy was not done. These specimens showed myeloid hyperplasia and infiltration, tending to exonerate Myleran toxicity.

COMMENT

Chronic myelocytic leukemia has been treated traditionally with x-rays.[10] Chemotherapeutic agents such as potassium arsenite (Fowler's) solution, nitrogen mustard, triethylenemelamine, 6-mercaptopurine, and urethan,* as well as radioactive phosphorus † have also been used. All have been attended by some measure of improvement on clinical and laboratory grounds. None has been curative, but some have been very useful. Dangerous, or simply annoying, side-effects of therapy, or the expense and inconvenience incident to the special equipment and specially trained personnel necessary for radiation therapy are practical considerations which have detracted somewhat from the benefits of treatment with these agents. In some cases these considerations have limited their availability to patients.

In our experience the response to Myleran therapy has been at least equal to that expected from x-ray therapy ‡ or radioactive phosphorus § and superior to that obtained with other chemotherapeutic agents.|| The gratifying symptomatic improvement, reduction in splenomegaly, restoration of normal blood values without resorting to transfusions, and the simplicity and convenience of ambulant therapy by means of daily oral medication, free from unpleasant side-effects and adequately controlled by weekly to triweekly office visits and blood counts are some of the points in favor of Myleran.

Treatment using 4 mg. daily, or on occasion 6 mg. daily, continuing until the leucocytes fall below 10,000 per cubic millimeter, gives satisfactory results, allows for adequate control, and minimizes the hazards. The larger the daily dose of Myleran the more quickly and dramatically does the leucocyte count fall. However, there is a like increase in the risk of toxicity. It would be most satisfactory if the variables could be taken into account for each patient and one could select with assurance that dose which would most expeditiously achieve the desired result with a minimum risk. The possibility that a clinically useful relationship exists between the dose of Myleran and the response thereto led to the formulation presented earlier (Fig. 3). While it is recognized that the relationship which we hypothecated may be defined better after more evidence is available for correlative studies, it is presented now because this approach offers something more than a purely trial-and-error method of prescribing the medication for each patient. In practice, one might use the scheme proposed in Table 3. It remains to be learned from future experiences whether or not the

* References 3 and 10.

† References 11-16.

‡ References 17-19.

§ References 11-16.

|| References 3, 10, and 20-24.

rate constant (k) is the same for all patients when they are given the same dosage per kilogram body weight.

The relief of anemia, without the need for transfusions, has been most impressive. This has been observed to be associated with a transient brisk reticulocytosis [8] which would seem on first appraisal to be a paradoxical response to a myelodepressant drug. However, the increase in erythropoiesis occurs only when relatively small doses of such a drug successfully restore the exaggerated granulopoiesis to normal proportions. One may infer, then, that Myleran promotes erythropoiesis indirectly.

The simplicity of treatment belies the potency of the drug, however. It would be dangerous to omit frequent examination simply because the patient's clinical course is one of improvement. Suppression of myelopoiesis and erythropoiesis, the principal untoward effect, may be regarded as an extension of the primary pharmacological action of Myleran. In sufficient dosage this can cause aplasia of the bone marrow.¶ The therapeutic usefulness of the medication depends upon the differential response to it of granulocytes, platelets, erythrocytes, and lymphocytes; the depressant effect decreases in the order just given.

TABLE 3.—*Proposed Dosage Schedule for Myleran Therapy* *

Initial Leucocyte Count/Cu. Mm.	Dose, γ/Kg./Day	Dose, Mg./Day, for 70 Kg. Patient
50,000	65	4½
100,000	75	5
200,000	82	5½
300,000	86	6
500,000	90	6½

* Based on Figure 3 and designed to bring leucocyte count to 10,000 per cubic millimeter in eight weeks.

Thrombocytopenia has been considered to be the main hazard in treatment.# With this we would agree, for leucopenia is largely avoidable by the program of treatment we have used, and pancytopenia has occurred only once in our experience. It is noteworthy that, among our four cases with purpura, two were the only cases in which we exceeded the daily dose of 6 mg. Whether this was a significant factor in bringing about the untoward results cannot be stated conclusively. Galton [2] and Haddow [25] believe that daily doses of 10 to 100 mg., as originally used, are more likely to cause thrombocytopenia and pancytopenia than smaller amounts of the drug and for this reason now favor using 4 or 6 mg. per day (60γ/kg./day). The inference from our own experience is in keeping with this view.

Galton [2] reported remissions of 6 months or longer in 8 of 19 patients, the longest continuing after 21 months. However, the "duration of remission" was not defined and, apparently, in some cases at least, the interval from the start of initial therapy to the start of subsequent treatment at a time when relapse was advanced (hemoglobin 7.3 gm. per 100 cc., leucocytes 100,000 per cubic millimeter, gross splenomegaly) was accepted as the measure of the duration of remission, rather than the period of relative normality which follows treatment. In our cases, as we have mentioned, retreatment was begun before relapse was advanced. Even so, in our series the interval from the end of one course of treatment to the start of the next was 6 months or greater in seven of the nine patients who have been observed for 6 months or longer after the initial therapy; in the eighth patient, the interval was 10 days short of 6 months. Thus, although the interval between successive courses of treatment in our cases was not as long as the intervals Galton reported in some of his cases, our results can be considered to be as satisfactory. Furthermore, it is important to note that the intervals between successive courses do not necessarily become shorter and shorter.

We have not attempted maintenance therapy. It seems to us that it is simpler to continue therapy until a remission has been achieved and to stop therapy entirely thereafter rather than to attempt to find a maintenance dose which will not produce harmful

¶ References 1, 2, 4, and 25.

References 2, 4, and 6.

effects. Furthermore, such a policy allows the patient longer periods of freedom from the biweekly or triweekly examinations, or even more frequent checks, which continuous therapy would necessitate. In further support of this view, it may be pointed out that long remissions have been produced by interrupted therapy and that it has yet to be shown that maintenance therapy may not be harmful rather than helpful in that toxic effects or drug resistance may possibly be produced thereby.

Although the symptomatic and objective signs of improvement following therapy have been quite definite, our experience with Myleran has been too brief and the number of cases has been too small to allow a statement concerning the influence of this drug on longevity in patients with chronic myelocytic leukemia. Nor are we able to state whether Myleran would prove effective when radiotherapy is no longer useful, although Galton actually found this to be the case in five of his patients.[2] As is the case with acute leukemia, the natural variations in the course of the disease, coupled with impressive remissions associated with treatment in some instances, may create the impression that the over-all course of the disease has been lengthened for most patients. Such inferences concerning longevity should be avoided, for when one seeks to prove them [26] it becomes a difficult matter. Nevertheless, the favorable results to date suggest that Myleran may be at least equivalent to x-radiation and radioactive phosphorus in prolonging life,[15] and therefore further investigation is worthwhile.

In the light of our findings and those of other authors already cited, we have been using Myleran as the agent of choice in the treatment of chronic myelocytic leukemia. This drug shows sufficient promise, when administered as described herein, to commend its use and study by others. The usefulness of Myleran is sharply limited by its prominent myelodepressant action, so that it is not only valueless but potentially harmful in chronic lymphocytic leukemia. It has failed to benefit patients with acute leukemia.*

* References 2, 4, and 6.

SUMMARY

Myleran (1,4-bis[methylsulfonyloxy]butane), a sulfonic acid ester, has been used in the treatment of 16 patients with chronic myelocytic leukemia in a total of 40 courses. When it is administered in daily oral doses of 4 to 6 mg., symptomatic improvement, normalization of the blood findings, and reduction—in many cases, disappearance—of splenomegaly can be achieved. Remissions continue in some patients for 6 to 12 months. The duration of therapy depends upon the individual response and generally can be expected to be about 40 to 90 days, the longest periods being required in patients with the highest initial leucocyte counts. Weekly to triweekly examinations of the patient and his blood suffice to guide therapy and, in most cases, to avoid the complications of thrombocytopenia and pancytopenia, which are considered to be the result of excessive dosage.

Dr. Donald S. Searle, Burroughs Wellcome & Company, Inc., supplied us with Myleran, and Misses Doris Kurth, Mitsue Yanagita, and Gwen Trappett gave technical assistance.

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Observations on the Regulatory Mechanisms of Aldosterone Secretion in Man

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The regulatory mechanisms governing aldosterone secretion in man are as yet obscure. Axelrad and Leutscher [1] have shown that a fivefold increase in urinary aldosterone occurs in man when the dietary sodium is restricted. Laragh and Stoerk [2] have suggested that serum potassium is a powerful direct or indirect stimulus to aldosterone secretion and that increases in urinary aldosterone on dietary sodium restriction are mediated by an alteration in serum potassium or Na/K ratio. Although corticotropin does not appear to affect either the excretion * or the blood levels of aldosterone in normal persons,[4] Gordon and co-workers [5] have found an increase in the output of this sodium-retaining hormone in a patient with rheumatoid arthritis following the intravenous administration of corticotropin. Leutscher and Axelrad [6] have observed essentially normal levels of urinary aldosterone in patients with panhypopituitarism. It has been suggested by Peters [7] that the mineralocorticoid output of the adrenal is under the control of volume receptors in the hypothalamus.

Studies by Leaf and his collaborators [8] in normal subjects on an adequate fluid intake show that administration of vasopressin (Pitressin) tannate in oil results in water retention, weight gain, hemodilution, and a marked increase in urinary sodium and chloride excretion. On cessation of vasopressin administration there occurs a water diuresis, with weight loss, a return of the serum concentrations to control levels, and a decrease in urinary sodium and chloride excretion to levels below the control. These investigators suggested that the observed changes could be related to alterations in adrenal cortex function. These studies have been repeated, and measurements of the urinary formaldehydogenic steroids, 17-hydroxycorticosteroids, and aldosterone have been made in order to determine the response of the adrenal cortex to changes in water and electrolyte metabolism under these conditions.

METHODS

Metabolic studies were carried out in two normal medical students admitted to the metabolism ward of the Royal Victoria Hospital. The subjects were maintained on a constant diet composed of 91 gm. of protein, 101 gm. of fat, and 221 gm. of carbohydrate (2200 Cal.). The sodium, potassium, and chloride intake was 217, 128, and 245 mEq. per 24 hours, respectively. A constant daily fluid intake of 4000 ml. was given except on the day when early symptoms of water intoxication developed as a result of vasopressin administration. After an initial control period, vasopressin tannate in oil was injected intramuscularly in a dose ranging from 2.5 to 15.0 units per 24 hours. Retention of water occurred in both subjects; in one a spon-

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* References 1 and 3.

taneous diuresis occurred during vasopressin administration, which was followed by repeated antidiuresis when the hormonal dose was increased.

The urine was collected in 24-hour amounts and the following determinations were made: sodium, potassium, chloride, creatinine, nitrogen, and specific gravity. The analytical methods used have been described in a previous communication.[9]

Total corticoid (free and conjugated) excretion was measured as formaldehydogenic steroids[10] and as 11,17-dihydroxycorticosteroids, by the Porter-Silber method.[11] Urinary aldosterone was determined by a modification of the procedure of Singer and Venning.† The urine was acidified to Ph 1.5 and extracted immediately with chloroform and again after it had stood at room temperature for 24 hours. The pooled chloroform extracts were washed with N/10 NaOH and water. After evaporation of the chloroform, the residue obtained was applied on paper and run in the Bush B_5 chromatographic system (benzene-methyl alcohol-water). The area of paper extending from the hydrocortisone

† References 12 and 13.

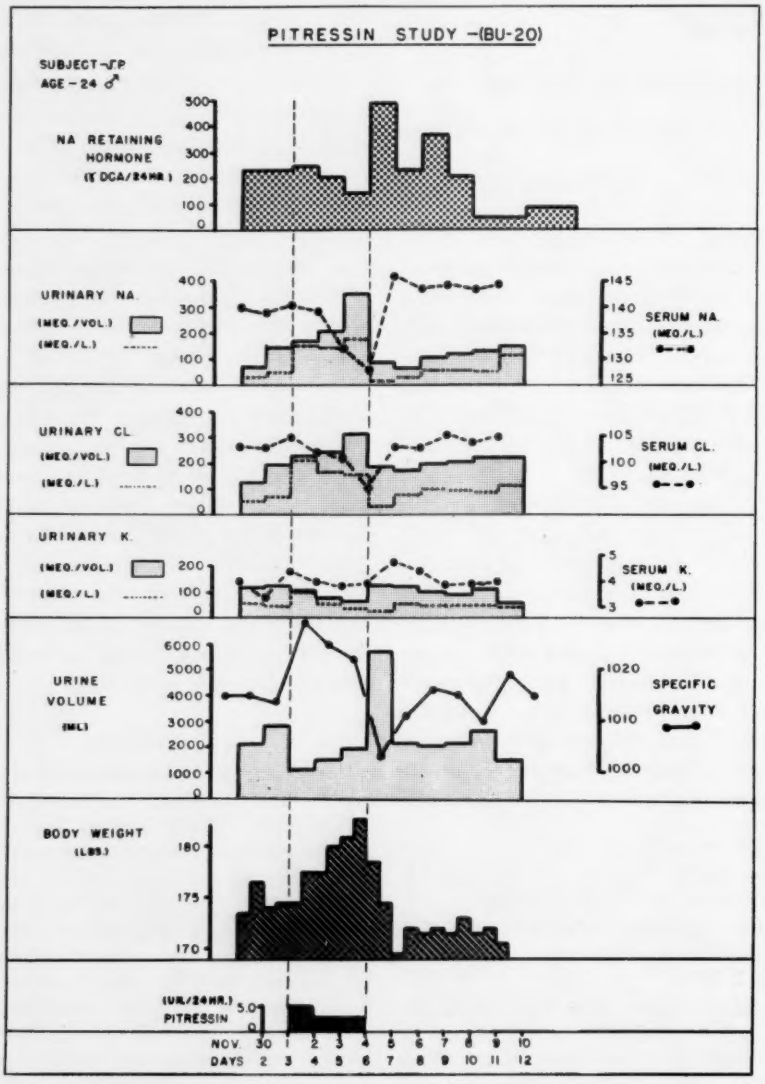

Fig. 1.—Alterations in electrolyte and water excretion and urinary aldosterone during vasopressin administration.

zone to and including the cortisone zone was removed and eluted. This extract was assayed in adrenalectomized rats for sodium-retaining activity, and an aliquot equivalent to a 40-minute volume of urine was administered to each rat. Ten animals were used per group. The sodium-retaining activity is expressed in micrograms of desoxycorticosterone acetate.

Hemoglobin, red blood cell count, hematocrit value, and serum sodium, potassium, and chloride were determined daily. Blood volume determinations,‡ with use of I^{131}-labeled albumin, were carried out at suitable intervals in an attempt to estimate the changes occurring in plasma volume.

‡ Dr. M. Dufrense performed these determinations.

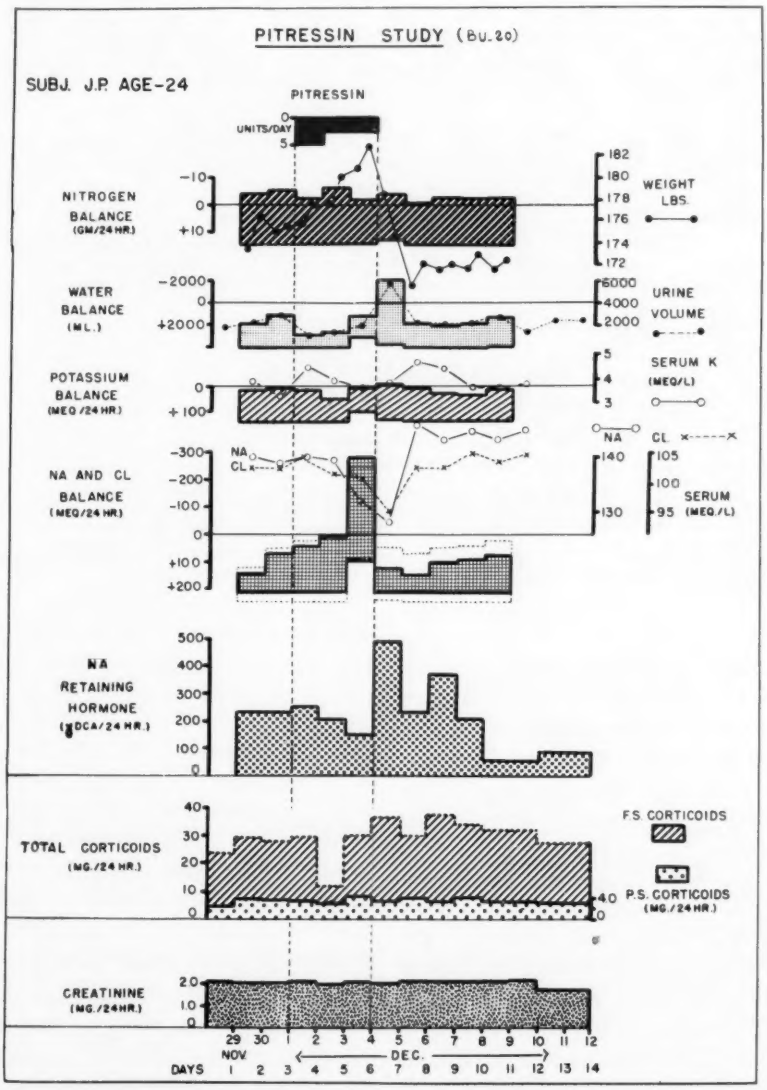

Fig. 2.—Metabolic balance data during vasopressin administration. There is a horizontal base line at zero. The intake is charted downward from this base line. The urinary and fecal excretions are then measured upward from the intake line toward the base line. If the output exceeds the intake, the final level will be above the base line; if the output is less than the intake, the final level will be below the base line. Thus a negative balance is indicated by a shaded area above the base line, and a positive balance by a clear area below the base line.

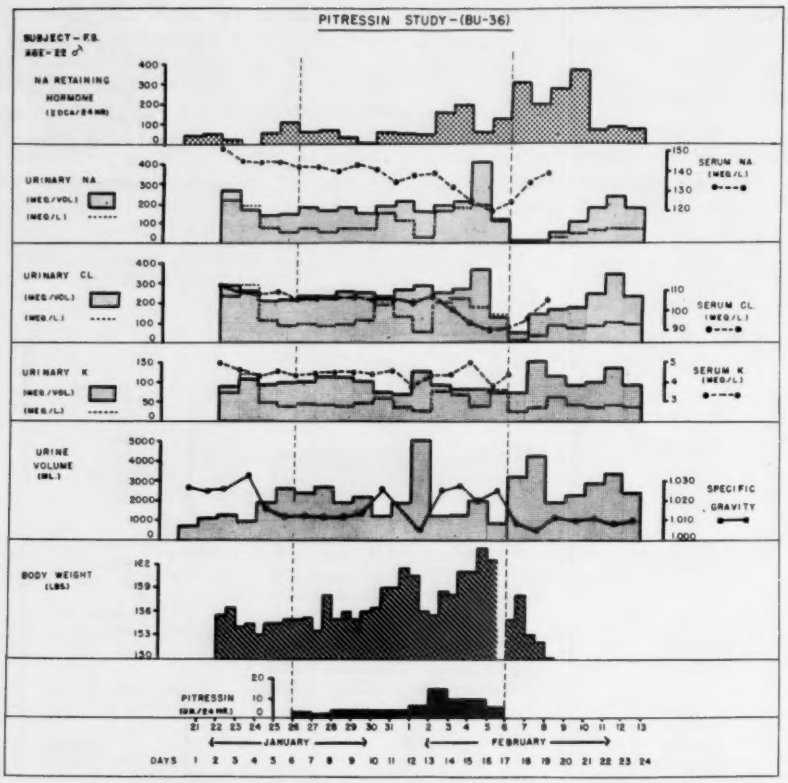

Fig. 3.—Alterations in electrolyte and water excretion and urinary aldosterone during vasopressin administration. Note the diuresis occurring on Day 12.

RESULTS

The response of Subject J. P. is shown in Figures 1 and 2. This student received an initial dose of 3.75 units of vasopressin tannate in oil intramuscularly followed by 1.25 units every 12 hours for three days (total dose, 10 units). The administration of vasopressin resulted in an immediate decrease in urine volume and a progressive increase in body weight. The concentration as well as total output of sodium and chloride in the urine increased, reaching a value of 350 and 315 mEq. per 24 hours, respectively, on the third day of vasopressin administration (sixth day of study). There was an accompanying decrease in the serum sodium and chloride to 128 and 95 mEq. per liter, respectively, at 8 a. m. on the seventh day.

During the first 24 hours following the cessation of vasopressin administration a diuresis (5700 ml. urine) occurred, with a return of body weight to slightly below normal value. The urinary sodium decreased from 350 to 66 mEq. per 24 hours, and the chloride, from 315 to 170 mEq. per 24 hours. A prompt return of serum sodium and chloride to normal levels occurred 24 hours after vasopressin withdrawal. During this period urinary aldosterone excretion increased to a value equivalent to 490γ of desoxycorticosterone acetate (DCA) per 24 hours with, P value < 0.001 when compared with the preceding day.

The changes occurring in the hemoglobin, hematocrit value, and total proteins during vasopressin administration suggested hemodilution, which was confirmed by an increase in the plasma of volume of 321 ml. on the sixth day, with no significant change in the red cell mass.

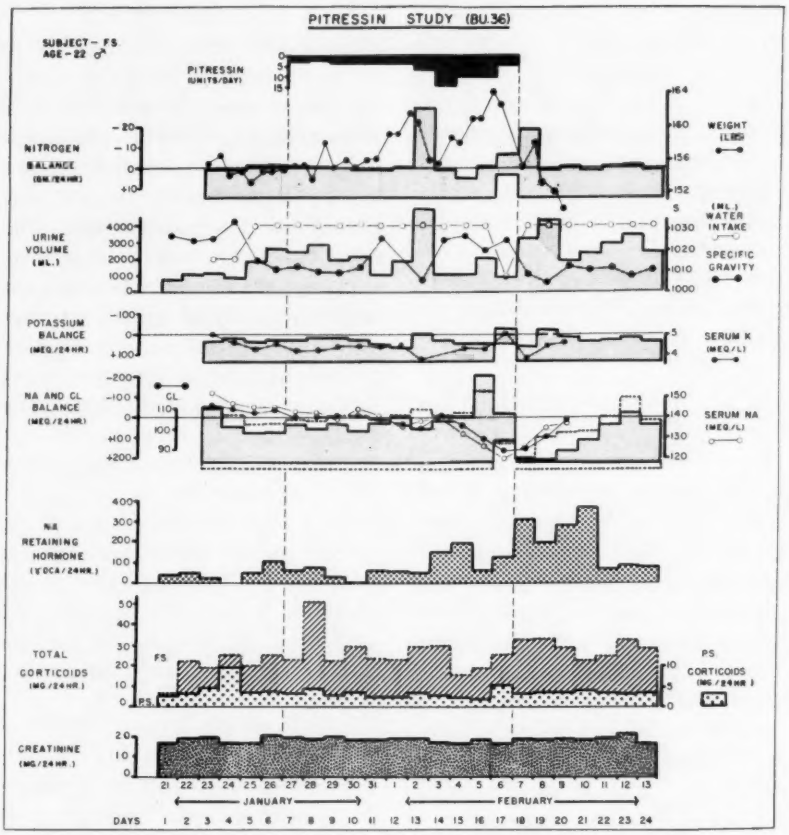

Fig. 4.—Metabolic balance data during vasopressin administration.

In Figure 2 are shown the over-all metabolic balance data. In addition to the variations in sodium and chloride there appeared to be no significant change in the potassium and nitrogen balance. The total formaldehydogenic steroids and 11,17-dihydroxycorticosteroids showed no definite trend in excretion pattern, in contrast to that observed in the aldosterone fraction.

In Figures 3 and 4 are charted the results of the metabolic studies carried out in Subject F. S. On an initial dose of vasopressin tannate in oil of 3 units per 24 hours, the expected fluid retention did not occur. On the fifth and sixth day of pitressin injection, when the dose had been increased to 4 units per 24 hours, the urine volume decreased from a mean of 2700 ml. to 1300 ml. per 24 hours and a resultant weight gain occurred. The sodium and chloride concentration in the urine rose, and there was a tendency toward a negative sodium and chloride balance. The serum sodium fell to 136 mEq. per liter.

On the seventh day a diuresis (5 liters of urine) occurred in spite of an increase in the vasopressin dosage to 7 units. The urinary sodium concentration decreased from 110 to 35 mEq. per liter; the total sodium, from 220 to 160 mEq. per 24 hours. The total urinary potassium increased 60 mEq. per 24 hours. These changes are mirrored in the balance data, where there was a retention of 60 mEq. per liter of sodium and a loss of 60 mEq. per liter of potassium.

On the 8th, 9th, 10th, and 11th days of vasopressin administration the dose was 15,

10, 10, and 5, units, respectively. This resulted in a second decrease in urine volume and an associated weight gain of 8 lb. in three days. During the last day of vasopressin injection the total urinary sodium and chloride reached a maximum value of 420 and 370 mEq. per 24 hours, respectively, with a negative balance of 205 mEq. of sodium and 125 mEq. of chloride. The serum sodium and chloride fell to 120 and 90 mEq. per liter, respectively, and the metabolic disturbance was accompanied by symptoms of water intoxication.

Cessation of vasopressin administration led to the same findings as in the first subject. In spite of a urine volume of 3300 and 4300 ml. during the first and second days after the vasopressin administration, the total urinary sodium fell below 20 mEq. per 24 hours.

In the control period and the days of vasopressin unresponsiveness the urinary aldosterone ranged between 0γ and 120γ equivalents of DCA per 24 hours, with an average of 55γ. After the spontaneous diuresis the levels increased to 155γ and 194γ equivalents of DCA (*P* value, 0.05) and then decreased at the time of the peak of urinary sodium excretion, caused by the administration of vasopressin. Following withdrawal of this hormone the serum sodium and chloride returned to normal levels. This was accompanied by a decrease in the excretion of these electrolytes and an increased output of urinary aldosterone. The changes in the hemoglobin, hematocrit level, and total proteins were similar to those seen in the first subject.

In Figure 4 are charted the metabolic balance data in Subject F. S. There was a slight change in the potassium balance. The two periods of negative nitrogen balance which occurred on Days 13 and 18 were associated with large urine volumes, but there was no significant change in the total corticoid excretion at this time. There was no alteration in the excretion of formaldehydogenic steroids and 17-hydroxycorticosteroids associated with the changes observed in electrolyte and water balance and no correlation with the excretion of aldosterone.

COMMENT

The limited data presented do not permit definite conclusions to be drawn. The changes in water and electrolyte balance described by Leaf and his associates [8] in response to the intramuscular administration of vasopressin tannate in oil have been confirmed in two normal subjects. The physiologic mechanism concerned with the alteration in urinary aldosterone excretion in response to vasopressin administration is not clear, but several hypotheses may be advanced. One is that the alterations are a direct effect of vasopressin. Leaf [8] first showed the dissociation between the rapid antidiuretic effect of vasopressin and its late effect on electrolyte excretion. These data suggest a similar dissociation between vasopressin administration and aldosterone excretion. The maximum effect on aldosterone excretion is seen after cessation of the vasopressin administration. In the second subject there was no significant change in aldosterone excretion during the period of vasopressin unresponsiveness. The spontaneous diuresis was followed by an increase in urinary aldosterone. Increasing the vasopressin dosage had no apparent effect on the aldosterone level.

A second possibility is that the increased aldosterone excretion occurring on withdrawal of vasopressin is a response of the adrenal cortex to a sodium depletion. An attempt to conserve sodium by the organism calls forth increased aldosterone production. If this is so, it is difficult to understand that there is no increase in aldosterone excretion during vasopressin administration, particularly at the peak of the negative sodium balance. This does not support the concept proposed by Laragh and Stoerk,[2] since serum potassium levels were normal throughout the period of observation. No relationship between the serum potassium and urinary aldosterone excretion is demonstrated.

A third hypothesis is that alterations in aldosterone secretion occur in response to alterations in the volume of one of the body compartments. In Subject F. S., during the

24-hour period after the spontaneous diuresis, urinary aldosterone excretion increased coincident with the fall in body weight; there was no significant alteration in serum sodium balance at this time. This is in agreement with Leaf's suggestion that the alteration in electrolyte excretion is secondary to alterations in hydration and would support the concept that aldosterone is dependent upon similar factors. Liddle and co-workers [14] have confirmed our findings and have suggested that volume changes and not changes in concentration or in total body sodium mediate the effect of sodium on aldosterone secretion. The present data do not allow us to choose between the last two hypotheses, but we favor the latter possibility.

SUMMARY

Vasopressin (Pitressin) tannate in oil was administered to two normal subjects on a complete metabolic balance study with a total fluid intake of 4000 ml. per day.

Vasopressin produced water retention and an increase in body weight which was accompanied by an increased urinary excretion of sodium and chloride and a progessive fall in serum sodium and chloride.

Cessation of vasopressin administration resulted in diuresis, with a loss of body weight and a decrease in the urinary sodium and chloride excretion. The serum concentration of these electrolytes gradually returned to normal.

Urinary aldosterone excretion increased after vasopressin withdrawal, returning to the control levels in four to five days.

There was no correlation between urinary corticoid excretion as measured by the formaldehydogenic and Porter-Silber methods and the changes observed in electrolyte and water excretion during vasopressin administration.

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Indefinitely Prolonged Chemotherapy for Tuberculosis

An Appeal

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Tuberculosis of the lungs is the most important and most insidious of the relapsing infections. Often without symptoms or signs of activity for years, it characteristically surprises patient and physician by exploding without warning from so-called "stability" into grossly progressive disease. It may then become quiescent again, only to repeat the cycle months or years later. Sometimes the process is repeated several times, to terminate fatally decades after the first episode. Thousands of patients have thus died of small improvements followed by fresh bronchogenic disseminations which could not be anticipated.

It has always been true that some patients recover and remain well. This was the case prior to chemotherapy. The incidence of relapse, however, in the prechemotherapy era, ranged from 24% to 56% in treated cases.*

It has become clear in the last several years that chemotherapy has an important role in the treatment of all cases of active tuberculosis. Such therapy too, however, may be followed by relapse or exacerbation after drug treatment has been stopped. The period 1946-1952, when short-term chemotherapy was practiced universally, is too recent for complete evaluation of results, but the literature documenting the occurrence of relapse in a considerable percentage of patients is growing.† A review of patients discharged as "arrested" from the Montefiore Hospital, Westchester Division, in the year 1951 showed that 15% already had relapsed by February, 1955.‡ One-third of all our admissions continue, as in years past, to be patients who have previously been treated for tuberculosis one or more times in an institution.

All clinicians who treat tuberculosis can recall cases of relapse after termination of apparently successful chemotherapy. Two examples are shown in Figures 1 and 2.

The confident prediction of which cases will relapse and which will not has never been possible. In a recent paper Medlar states,[13] "The greatest difficulty is that the crudity of present methods does not permit the behavior of residual necrotic lesions to be determined

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* References 1-6. In a 20-year follow-up, Dr. Roger Mitchell found a primary relapse rate of 30% in patients discharged from Trudeau Sanatorium after attainment of control of the disease. Seven-eighths of the relapses occurred in the first five years after discharge. (Personal communication to the authors.)

† References 7-12. Katz, H. L.: Recrudescence of Tuberculous Disease in Cases Treated with Early Streptomycin-Para-Aminosalicylic Acid Regimens: A Clinical, Roentgenographic and Pathologic Study, Reference 11, p. 148; Raleigh, J. W.; D'Esopo, N. D.; Osgood, C. K., and Campbell, A. M.: Relapse Following Streptomycin-Para-Aminosalicylic Acid Therapy for Pulmonary Tuberculosis, Reference 11, p. 144.

‡ Dr. Hans Abeles and the New York City Department of Health assisted in obtaining these data.

at the time clinical health has been regained. However, this difficulty is not new. This feature has always made the behavior of pulmonary tuberculosis unpredictable." Prognosis is impeded by lack of reliable clinical or serological tests for inactivity of lesions. Further, x-ray shadows consistent with "stability" may be misleading. Negative sputum and gastric or bronchial secretions are unreliable; inability to demonstrate tubercle bacilli on culture or guinea pig inoculation is frequently observed in patients with active disease who are receiving antimicrobial drugs.

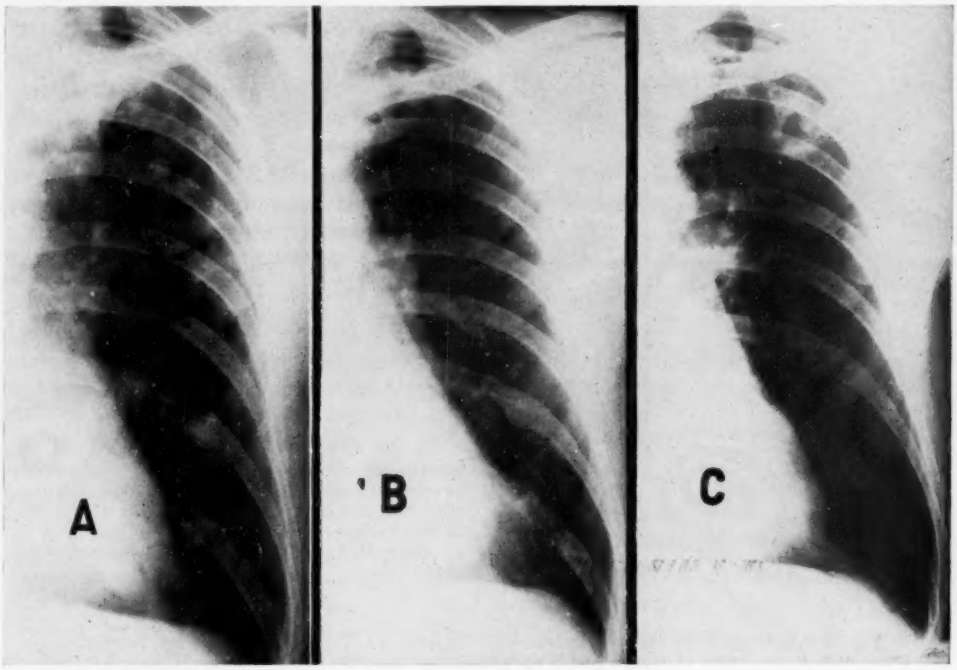
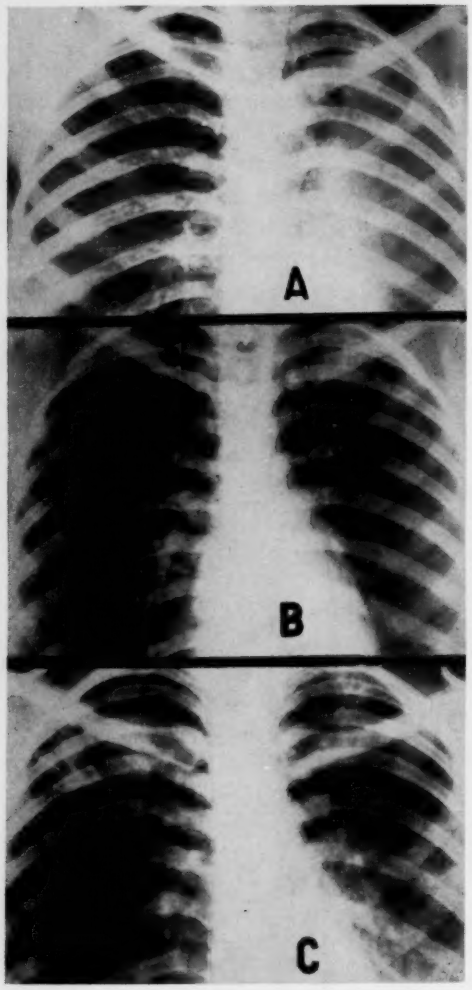


Fig. 1.—*A*, x-ray of 44-year-old white man with cavitary tuberculosis, left upper lobe. *B*, apparent closure of cavity, confirmed by tomography, after treatment with bed rest and streptomycin-PAS for 10 months; gastric cultures were negative. *C*, relapse with cavitation and positive sputum one and one-half years later.

Relapses take place even after the offending (i. e., visible) lesion has been removed surgically (Fig. 3). Exacerbations occur in lobes or segments which appeared normal roentgenographically and which felt normal to the surgeon's palpating fingers at the time of operation. The pathogenesis of pulmonary tuberculosis makes it unlikely that all the potential sources for "reactivation" can be excised from the human host. Helpful and necessary as it is to resect grossly caseous or cavitary lesions, there still remain potentially dangerous foci, microscopic or larger, containing viable tubercle bacilli, in other segments of the lungs, in the bronchial tree, in the draining lymph nodes, or in distant organs. Persistence of positive skin-reactions to tuberculin after resections is the rule, a fact constituting further evidence that living tubercle bacilli remain in the body.

CLINICAL DATA

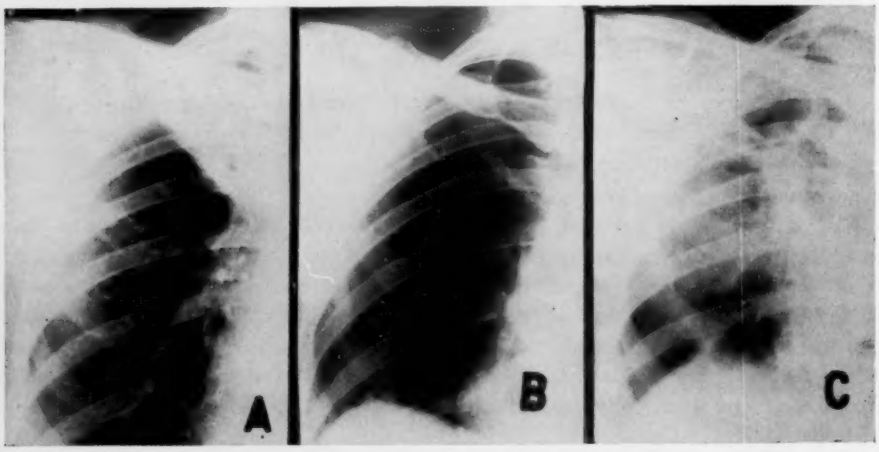
Prolonged Chemotherapy.—The availability of combinations of drugs which effectively and reciprocally postpone emergence of bacterial resistance makes it possible to continue chemotherapy for prolonged periods. We have followed 172 consecutive discharged patients who have now been maintained on



uninterrupted combined chemotherapy for periods of 12 to 45 months. These patients, ranging in age from 14 to 77 years, were all receiving their first courses of drug therapy for tuberculosis. One hundred sixty-one suffered from active pulmonary tuberculosis (30 minimal, 111 moderately advanced, and 20 far-advanced); 11 had active predominantly extrapulmonary tuberculosis. Fifty-three have now been treated for 12 to 23 months; 96 have been treated 24 to 35 months, and 23 have been treated without interruption for more than 3 years. The mean duration of chemotherapy is now 27+ months. All the patients received combinations of streptomycin-*p*-aminosalicylic acid (PAS), isoniazid-PAS, streptomycin-isoniazid, or streptomycin-isoniazid-PAS and were treated on modified bed rest until gross signs of activity had disappeared. They were then made ambulatory, and after gradual rehabilitation they returned to work or school. Pulmonary resections were done where indicated (in 31 patients, 18% of the total). In all patients—resected and unresected—chemotherapy was

Fig. 2.—*A*, x-ray of 17-year-old Negro girl with tuberculous involvement of left lung, tuberculous bronchitis, sputum positive. *B*, marked improvement after bed rest and chemotherapy for 11 months; gastric cultures were negative. *C*, relapse with extensive spread to left lower lobe and right lung four years later.

Fig. 3.—*A*, x-ray of 50-year-old woman with involvement of right upper lobe and tuberculous bronchitis. *B*, resection after short-term chemotherapy; remainder of lung parenchyma is clear roentgenographically. *C*, relapse with extensive involvement of residual right lung three and one-half years later.



continued after their return home and to physical activity. Patients receiving streptomycin were taught to inject the drug themselves intramuscularly, or they received their injections at home from visiting nurses. All the patients were followed clinically, roentgenographically, and bacteriologically in the outpatient department or by their personal physicians. There has been relapse or exacerbation of the tuberculosis in three of the entire group, a relapse rate of only 1.7%. These cases are presented here.

CASE 1.—A white man was discharged from the hospital with patent cavity and positive sputum after seven months of chemothrapy. Pulmonary resection would have been performed had there not been the cumulative contraindication of emphysema, calcific aortic stenosis, and manic-depressive psychosis in a 60-year-old man. His cavity remained open, and there was bronchogenic spread 10 months after discharge. His disease is progressive, and he is now a patient in a psychiatric hospital.

CASE 2.—A 30-year-old white man whose infiltrative pulmonary lesion responded satisfactorily, with conversion of sputum, was discharged after 11 months of chemotherapy. Six months later, after receiving streptomycin and PAS for 17 months, he stopped the drugs without notice and contrary to advice. Six months thereafter there occurred local extension of the lesion.

CASE 3.—An 18-year-old white woman whose minimal lesion responded well was discharged with negative gastric cultures after 10 months of chemotherapy. She then stopped taking her medication regularly "because of the inconvenience of carrying the tablets to work." Eight months after discharge progression of the lesion was seen in her roentgenograms.

The tubercle bacilli recovered from the sputum of Case 1 after the exacerbation were partially drug-resistant in vitro. This is frequently the case when cavitation and positive sputum persist under therapy. In Cases 2 and 3 no in vitro drug susceptibility tests could be done after relapse, because organisms could not be grown; both patients are again receiving chemotherapy.

Toxicity.—As indicated in an earlier communication,[47] we have not found it necessary in any instance to discontinue chemotherapy because of drug toxicity. Hypersensitivity to streptomycin or PAS is seen in about 2% of patients,§ early in treatment, and when this or severe gastrointestinal intolerance to PAS is encountered another agent is substituted. Streptomycin sulfate in dosage of 1 gm. two or three times weekly produces little or no eighth nerve damage in most patients.[15] In the older age group it occasionally produces troublesome vertigo, necessitating substitution of dihydrostreptomycin for the sulfate. Dihydrostreptomycin is more destructive to the cochlear division of the eighth nerve than is streptomycin sulfate, and when the former drug must be used audiometric tests should be done regularly. Other side-effects of streptomycin and PAS are observed infrequently.‖ Isoniazid has been in use for a much shorter period. The literature shows it to be relatively nontoxic in dosage of 3 to 5 mg. per kilogram of body weight per day over short periods of time.¶ We have found no increase in toxicity with this dosage when the drug is given for up to three years.

When streptomycin sulfate is administered some patients complain intermittently of headache, malaise, drowziness, or a mildly "drunk" or "hung-over" feeling on the day on which they receive the drug. We have previously called attention to this syndrome of streptomycin intoxication.[47] In order to evaluate more fully this type of reaction, 197 patients who were receiving streptomycin sulfate have been given an inert substance as a placebo.# All the injections of placebo were administered in the same week, each patient receiving one injection of placebo in place of one of the regular streptomycin injections. Nursing personnel, patients, and doctors did not know until after completion of the experi-

§ Schwartz, W. S., and Moyer, R. E.: The Incidence of Severe Toxic Reactions to Streptomycin and Para-Aminosalicylic Acid, Reference 14, p. 196; Warring, F. C., Jr., and Howlett, K. S., Jr.: Allergic Reactions to PAS, Reference 14, p. 192.

‖ References 16-32.

¶ References 33-46.

Supplied by Dr. Gladys Hobby, of Chas. Pfizer & Company, Inc., Brooklyn.

ment whether drug or placebo was being given. The patients were questioned by the same observer, using a uniform, standardized approach, as to effects of the injections. Reactions, usually mild, were attributed to streptomycin by 65 of the 197 patients and to the placebo by 39. Three of the latter described reactions to placebo which were equal to or greater than those they experienced from streptomycin administered during the same week; eight patients had reactions to the placebo and none at all to streptomycin. No reaction to either the drug or the placebo was reported by 124 patients. No definite correlation could be established between duration of drug treatment and the presence or absence of this type of reaction. There was evident, however, a tendency for patients close to each other in the hospital to react similarly to streptomycin, entire wards being almost entirely free of reactions at times. Apparently the psychic component and suggestibility play an important part. The physiologic component of the syndrome as observed by us has not been disabling.

COMMENT

Because the treatment of tuberculosis is always long-range, complete healing requiring years for its accomplishment,* chemotherapy should not be instituted before the diagnosis has been established beyond reasonable doubt. Once drug treatment has been begun, however, it should not be stopped without a positive indication. The situation at this time is analagous in many ways to that obtaining in the prophylaxis of rheumatic fever recurrences in persons having a history of rheumatic fever or evidence of rheumatic heart disease. The American Heart Association now recommends drug prophylaxis for rheumatics "throughout life, or until new knowledge makes this recommendation invalid." [50] In the patient with tuberculosis one is still unable to predict permanent cure. Prognostic indices are no better than they were prior to chemotherapy, although the outlook for all treated patients is now infinitely brighter. Drug treatment with presently available agents does not sterilize the lung.† Neither does surgical removal of all visible and palpable foci of tuberculosis. Relapses are observed after discontinuance of chemotherapy given for periods of time arbitrarily or empirically determined. On the other hand, relapse during continuation of drug treatment is rarely seen.

The reason for the value of prolonged chemotherapy in the prevention of relapse lies in the area of speculation. The source of relapse is the residual necrotic lesion. That virulent tubercle bacilli can survive in necrotic lesions is established,‡ but it is not known why rapid bacillary multiplication and softening of these lesions occur in some cases and not in others. It is not even known whether softening of caseous lesions precedes or follows rapid multiplication of organisms within them. If chemotherapy is being continued, bacterial multiplication in the caseous lesion may be reduced, the organisms may not thrive at a new site, or new lesions do occur without evolving to roentgenographically visible proportions.

It must be emphasized that failure to close cavities and convert sputum to negativity adversely affects the prognosis (as in Case 1 cited above) even if chemotherapy is continued indefinitely. Resection of cavities remaining patent after treatment, or their closure or filling-in by other methods or spontaneously, is an essential step in cure. Once this has been accomplished, however, relapse still may occur. In order to minimize this possibility, we consider it mandatory to continue drug administration unless drug toxicity absolutely requires termination or until continuing research and experience provide a guide as to when chemotherapy can safely be discontinued. The drugs now in general use can be given for years with much less risk to the patient than that inherent in the disease itself. In our experience, patient ac-

* References 48 and 49.

† References 51 and 52.

‡ References 51 and 52.

ceptance of this program is good when the physician himself is aware of its importance.

SUMMARY AND CONCLUSIONS

1. Treated pulmonary tuberculosis carries a high risk of relapse after apparent control of the disease. The incidence of "re-activation" or relapse prior to chemotherapy ranged from 24% to more than 50% in patients followed for 20 years after "arrest."

2. There are increasing indications that antimicrobial therapy for short periods of time does not prevent late relapse after chemotherapy has been terminated.

3. Active disease may become evident in other parts of the lungs or bronchial tree after surgical excision of all visible lesions.

4. Trustworthy prediction of which patients will remain well after termination of treatment is difficult, because of the lack of reliable criteria for inactivity of residual lesions.

5. A consecutive series of 172 patients discharged from the hospital but continued indefinitely on chemotherapy showed no relapse in 98.3% of the cases after 12 to 45 months of drug treatment.

6. Drug toxicity was never so severe as to necessitate cessation of treatment. By use of a placebo the symptoms of streptomycin intoxication were demonstrated to be due, in part, to psychic factors. There was no correlation between the duration of treatment with streptomycin and the occurrence of streptomycin intoxication.

7. Very prolonged therapy with various combinations of streptomycin, PAS, and isoniazid is practicable, relatively devoid of serious toxicity, and generally acceptable to properly indoctrinated patients. Since the optimal duration of drug treatment is not presently known, we believe that chemotherapy under close observation should be prolonged indefinitely except in the presence of threatening side-effects or until a reliable guide to termination of chemotherapy becomes available.

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Experiences with 2-Hydroxystilbamidine in Systemic Sporotrichosis

Report of An Unusual Case

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Systemic sporotrichosis involving the skin, bones, viscera, and central nervous system is rare.* Recent reviews of sporotrichosis make only passing mention of this unusual syndrome. Collins [3] has reported the case of a 67-year-old man with disseminated cutaneous and visceral lesions. Clinically, except for the cutaneous involvement, the patient was asymptomatic. Enlargement of the liver and spleen was noted on physical examination. At necropsy, however, multiple visceral lesions were observed in the form of microscopic miliary granulomas. The skin, lungs, spleen, liver, kidneys, adrenals, cerebral cortex, and bone marrow were involved. Cawley [1] has reported the case of a 70-year-old man who had multiple disseminated subcutaneous gummatous lesions and probable osseous lesions and who apparently was cured with iodides. Moore and Kile [14] reported a case of generalized subcutaneous gummatous ulcerating sporotrichosis with skin and pulmonary lesions which apparently cleared up with iodide therapy.

Involvement of the central nervous system with sporotrichosis evidently is extremely rare. In the patient reported by Collins,[3] the miliary lesions involving the cerebral cortex were unsuspected clinically and were found at necropsy. The patient reported on by Hyslop and colleagues [11] had chronic diffuse leptomeningitis which did not respond to iodide therapy; the organism was noted on smear only; it was not possible to grow out Sporotrichum schenckii on culture. That these two patients may not represent infections with S. schenckii will be commented on later. In an epidemic involving 2825 gold miners in South Africa, disseminated disease with involvement of the viscera or central nervous system did not occur.[23]

We are reporting an unusual case of apparently widespread systemic sporotrichosis, including involvement of the central nervous system, which was treated with 2-hydroxystilbamidine for 32 days.

REPORT OF CASE

History and Physical Examination.—A 60-year-old white man had worked in a cement, tile, and clay-producing factory for 17 years. At this occupation he had been exposed to much dust. One year prior to his coming to the Mayo Clinic a chronic indolent ulcer developed on one of his thumbs; this healed very slowly. Six months before admission he began to experience easy fatigability. One month before admission he noted the gradual onset of a "boil" on the inner aspect of the right thigh, which eventually broke down and drained purulent material one week later. As this "boil" cleared up, painless nontender subcutaneous nodules were noted on both sides of the neck, the body, and the four extremities. Two weeks before admission he began to have a moderately severe lumbar backache, which persisted throughout most of the period of observa-

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* References 5 and 16.

tion. One week before admission he noted some difficulty with speech, and three days before admission he noted transient, nearly complete blindness which occurred several times. This was followed by difficulty in performing fine movements with the right hand. He had experienced some loss of weight and slight progressive weakness, and he gave a history of slight productive cough of long standing.

Physical examination revealed nontender and relatively fixed subcutaneous nodules of various sizes up to 2 cm. in diameter, which were noted in the anterior cervical regions bilaterally, the mid-anterior part of the left arm, the extensor surface of the right forearm, the anterior surface of the right thigh, the abdomen, and the lower part of the back. The two nodules that were present over the left biceps muscle appeared discrete and measured 1 to 1.5 cm. in diameter. Auscultation of the heart revealed a minimal aortic systolic murmur. The lower edge of the liver extended to the level of the umbilicus. The spleen, however, was felt only 1 or 2 fingerbreadths below the left costal margin.

During the preliminary examinations, while the patient was ambulatory, the dysarthria developed into an almost complete expressive aphasia and the right arm became paretic and finally almost completely paralyzed. With this progression of the disease, the patient was hospitalized for further investigation and therapy.

Laboratory and Special Examinations.—The initial routine laboratory data were as follows: The concentration of hemoglobin was 14.3 gm. per 100 cc. of blood. The erythrocyte count was 4,700,000 and the leucocyte count 11,200 per cubic millimeter, with an essentially normal differential count. An occasional cell with myeloid immaturity was seen in smears of the peripheral blood. Urinalysis revealed slight albuminuria, microhematuria and micropyuria, and occasional casts; there was no Bence Jones protein. Excretory urography, cystoscopic examination, and left retrograde pyelography disclosed a grossly normal urinary tract. A blood flocculation reaction for syphilis was negative, and the erythrocyte sedimentation rate was 24 mm. in one hour (Westergren method). The concentration of blood urea, blood calcium, serum bilirubin, and total serum proteins and the albumin-globulin ratio were within normal limits. A liver-function test with sulfobromophthalein (Bromsulphalein) revealed Grade 1 retention (8%) at the end of one hour. A blood-agglutination test for brucellosis gave negative results, but a blood-agglutination test for tularemia gave positive results in a dilution of 1:160. Two routine blood cultures showed no growth after 2 days and after 20 days.

X-ray examination of the thorax disclosed a fine nodular fibrosis that was evenly distributed throughout both pulmonary fields. Sputum examinations for acid-fast bacilli, fungi, and tumor cells gave negative results. Bronchoscopy likewise gave negative results. No malignant cells or pathogenic organisms were found in the bronchial secretions. Skin tests were negative for tuberculosis, coccidioidomycosis, and histoplasmosis. X-ray examination of the head and the lumbar portion of the spinal column revealed no destructive changes. The pressure of the spinal fluid and ventricular fluid, as well as the cell count and value for protein, was normal; routine cultures and special smears and cultures for acid-fast bacilli and fungi did not disclose any micro-organisms. Smears of the sternal bone marrow appeared normal; in the fixed sections a tremendous increase in megakaryocytes in all stages of development was observed, the cells being arranged in nests and simulating granulomatous lesions. Cultures of the bone marrow for acid-fast bacilli and fungi were negative. Five biopsies were performed on the subcutaneous nodules, from one of which S. schenckii was cultured; all the nodules were negative on culture for Brucella and acid-fast organisms.

Treatment with 2-Hydroxystilbamidine.—With the isolation of S. schenckii, it was thought that all the manifestations of disease in this case could be explained on the basis of generalized (that is, visceral) sporotrichosis with involvement of the central nervous system. It was decided to treat the patient with 2-hydroxystilbamidine.† Accordingly, he was started on treatment with 200 mg. of the drug dissolved in isotonic saline solution and administered daily by slow intravenous drip over a period of 45 to 60 minutes. After 15 days the dose was increased to 250 mg., and this dose was continued for the remainder of the 32 days of treatment. For two days prior to the start of therapy, the patient's temperature had risen to 102.4 F. With therapy, the temperature decreased to normal in two days, the patient's general condition improved, and slight, but definite, objective improvement occurred in his ability to speak and in the strength and movements of the right arm.

Therapy with 2-hydroxystilbamidine was uneventful until the 30th day, when the development of widespread intense pruritus necessitated stopping of the intravenous medication before the full dose had been given. The same reaction recurred on the 31st and 32nd days of treatment, and so it was necessary to stop treatment entirely for a few days. Six and seven days later, the drug was given again, but very slowly. The same intense pruritic reaction came on after 25 or 30 drops of the medication had been given, and the infusion had to be stopped. Skin tests were then performed with 2-hydroxystilbamidine on the patient and on a control patient who had not received the drug. A tenth of a cubic centimeter of solution containing

† The 2-hydroxystilbamidine was supplied by the Wm. S. Merrell Company, Cincinnati.

1 mg. of 2-hydroxystilbamidine per cubic centimeter of isotonic saline solution was injected intracutaneously. This produced a wheal 1 cm. in diameter. The wheal was surrounded by an area of erythema 3 cm. in diameter. A control injection of 0.1 cc. of isotonic saline solution in the other arm of the patient produced no reaction. Similar tests performed on the control patient, who had not been given 2-hydroxystilbamidine, produced only a small wheal, measuring 0.75 cm., with surrounding erythema.

Despite the results of the skin test, it was thought that the patient should have further therapy with 2-hydroxystilbamidine if such was possible. Accordingly, after an interval of 10 days, the medication was given in solution with 20 mg. of chlorprophenpyridamine (Chlor-Trimeton) maleate. After 33 drops of the drug had been given by very slow intravenous drip, the patient experienced severe generalized pruritus which was followed promptly by pallor and mild cyanosis of the lips, dyspnea, substernal discomfort and tightness, sweating, and tachycardia. This alarming anaphylaxis-like reaction subsided in five minutes after treatment with an additional 10 mg. of chlorprophenpyridamine maleate and 0.1 cc. of 1 : 1000 dilution of epinephrine given intravenously.

During therapy with 2-hydroxystilbamidine the patient's eosinophile count rose from the vicinity of 3% to 5% to 15%. This observation, together with the positive skin reaction and the severe reaction to further treatment with the drug, led to the conclusion that an allergic sensitivity to 2-hydroxystilbamidine had developed and that further administration of it was precluded. No other toxic reaction from the 2-hydroxystilbamidine was noted.

Also, during therapy with 2-hydroxystilbamidine, urinalysis; blood-urea determination; liver-function tests, including e of sulfobromophthalein; the several flocculation tests, and determination of the total serum proteins, the albumin-globulin ratio, the prothrombin time, and the serum bilirubin were made at weekly intervals, and these showed no alteration from the initial values. The sulfobromophthalein test showed an unvarying 6% to 8% retention of the dye throughout therapy. The results of other liver-function tests remained within normal limits. No toxicity to 2-hydroxystilbamidine occurred other than the development of allergic sensitivity.

Interval Between 2-Hydroxystilbamidine Therapy and Iodide Therapy.—During a three-week interval between the termination of 2-hydroxystilbamidine therapy and the start of iodide therapy, the patient's neurologic improvement was maintained. With 2-hydroxystilbamidine therapy the subcutaneous nodules almost completely disappeared in the first two weeks of treatment, and only slight, apparently fibrotic, residues remained for another week or two. About a week after the 2-hydroxystilbamidine therapy was discontinued, the patient began to experience daily one to five momentary episodes of motor weakness, numbness, and paresthesia in the left hand and forearm. Between attacks the neurologic manifestations of the left extremity were normal.

During the interval between treatment with 2-hydroxystilbamidine and treatment with potassium iodide, subcostal needle biopsy of the liver and splenic puncture were performed. Histologic examination of the splenic material revealed a picture compatible with infectious splenitis, and culture of this material for S. schenckii gave negative results. Histologic examination of two specimens of hepatic tissue revealed granulomatous hepatitis with a few portal-space granulomas, scattered foci of chronic inflammatory cells in the lobules, and evidence of mild cirrhosis; cultures of this tissue were negative for S. schenckii. Cultures of the splenic and hepatic material were negative for acid-fast bacilli and Brucella organisms.

Iodide Therapy.—Treatment with saturated solution of potassium iodide was begun on the 75th day of observation and continued during the last month of the patient's life. The initial dose was 10 drops (0.6 cc.) three times a day. This was gradually increased until the patient was taking 2 drachms (8 cc.) of the solution four times a day without evidence of intolerance or toxicity. Despite the increasing doses of iodide, the patient's motor aphasia worsened and the motor power in the right arm and hand lessened. The patient began to have pain and weakness in the right leg. He continued to have the transient episodes of weakness, numbness, and paresthesia in the left upper extremity, and he began to have a little drowsiness about a week before death. His condition then deteriorated rapidly, and he became comatose and died after being in coma 30 hours. He had been under observation and treatment for a period of 107 days and had had active disease for approximately 150 days.

Other Clinical and Laboratory Data.—Periodic x-ray examination of the thorax made during the course of the illness revealed no changes in the fine nodular fibrosis noted in the initial film, and it was concluded that this probably represented pneumoconiosis in view of the patient's occupation and long exposure to dust. Periodic x-ray examination of the spinal column revealed no changes from the initial films, although on one of the films taken toward the end of our observations the radiologist thought that there might be some evidence of destructive changes in the first sacral segment.

The erythrocyte sedimentation rate gradually rose during the patient's hospitalization to levels of 90 to 111 mm. in one hour. The concentration of hemoglobin was maintained during therapy with 2-hydroxystilbamidine but gradually fell from values

of 13.6 to 15 gm. per 100 cc. of blood to 11.7 gm. just before death. The leucocyte count varied during the course of the illness from 11,200 initially to 8900 midway during treatment with 2-hydroxystilbamidine, and it then rose to 18,700 and 15,100 during the last weeks of observation. After 2-hydroxystilbamidine therapy was terminated, the eosinophile count gradually decreased from the 15% value to normal.

Complete studies, including cultures for pathogens and fungi, made on fluid removed during ventriculography performed on the 80th and 103rd days of observation (after 2-hydroxystilbamidine therapy) gave negative results. Electroencephalograms obtained on the 14th, 70th, and 96th days of observation (before and just after 2-hydroxystilbamidine therapy, and during iodide therapy, respectively) revealed a dysrhythmia that suggested disturbance of cortical function in the left temporal area. The tracing taken immediately after 2-hydroxystilbamidine therapy showed slight improvement. The tracing taken during treatment with potassium iodide, when the patient was deteriorating, showed slightly greater dysrhythmia than did the initial tracing.

Neurosurgical opinion figured prominently in the management of this patient. After S. schenckii was isolated it was thought that the patient probably had diffuse systemic sporotrichosis with a focal left cerebral lesion. It was our opinion that if the disease proved amenable to systemic chemotherapy, then neurosurgical procedures would be considered only to handle problems of increased intracranial pressure, to avoid damage to the brain by removing the pressure effects of a circumscribed, expanding, focal lesion. When improvement occurred with 2-hydroxystilbamidine therapy, it was hoped that the intracranial process would resolve with further systemic treatment. When it became apparent that this process had not stabilized but was progressing, ventriculography was decided upon.

The first ventriculograms, made on the 80th day of observation, revealed dilatation of the entire ventricular system; the left lateral ventricle was more dilated than the right. This was consistent with a diffuse intracranial process rather than an expanding focal lesion. There seemed to be more atrophy of the left hemisphere than of the right. Consequently, neurosurgical measures did not seem advisable.

When the patient began to deteriorate more rapidly, four days before his death (that is, on the 103rd day of observation), ventriculography was performed again to determine whether or not focal expanding granulomatous lesions had formed and were producing increased intracranial pressure; the findings were grossly the same as those in the first ventriculographic examination. Because there was no evidence of a focal expanding lesion, neurologic operation was not deemed advisable.

Necropsy.—Gross Findings: The healed scars resulting from biopsies were the only cutaneous lesions. There was general wasting of the body. The lungs were moderately heavy, the right weighing 550 gm., the left, 500 gm. The pleural surfaces were covered by sometimes discrete and sometimes fusing areas of black pigmentation. On section, the lungs maintained their shape, and similar black nodules 1 to 4 mm. in diameter were distributed evenly throughout their substance. The trachea and major bronchi contained thick purulent material; the alveoli, a moderate amount of froth. The mediastinal lymph nodes were not enlarged but were rubbery and black.

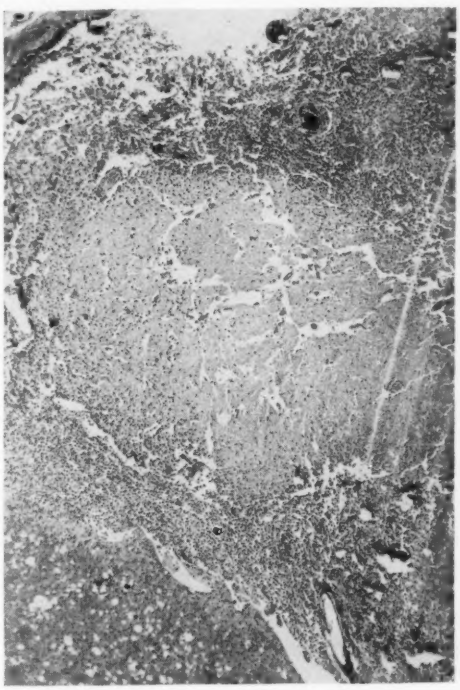


Fig. 1.—Section from a lesion in the left posterior parietal area showing subcortical area of granulation tissue with numerous gitter cells, nodules of calcification, and surrounding infarction. Hematoxylin and eosin; × 20.

The heart was moderately enlarged and weighed 485 gm. Dense white scar tissue partially replaced the muscle subendocardially in the posterior basal area. There was an old complete occlusion of the right circumflex coronary artery beginning 2 cm. from its origin and extending throughout the remainder of its length. The left coronary artery and its branches showed marked atherosclerosis but were without an area of complete occlusion.

The spleen was enlarged and weighed 425 gm. It had a mottled red smooth surface. On section,

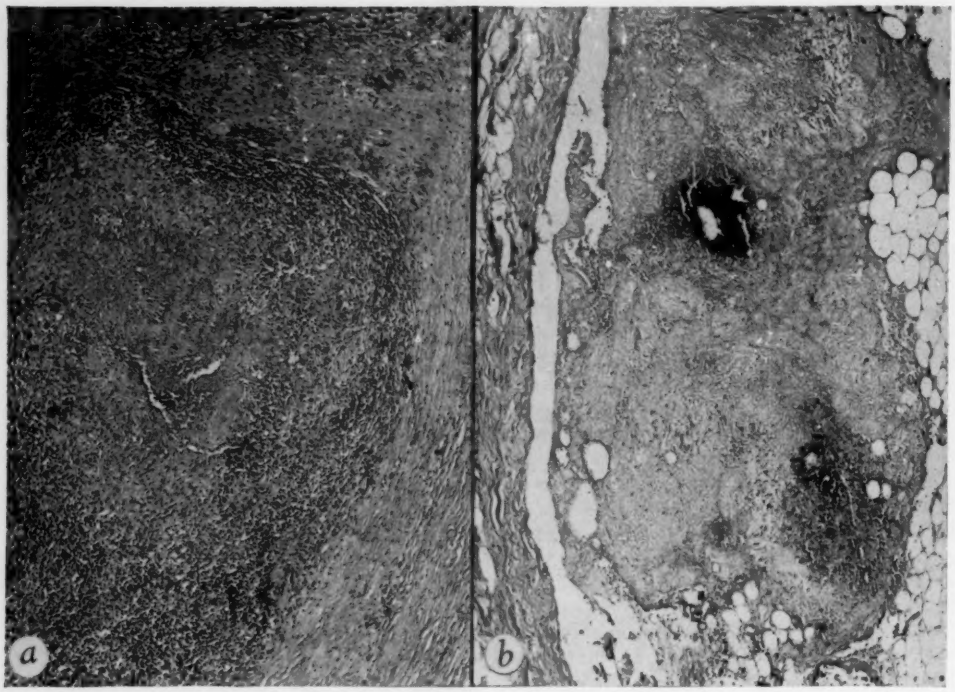


Fig. 2.—Sections from root of first sacral nerve. (*a*) Healing granuloma with outer layer of fibrous tissue, inner layer of lymphocytes and mononuclear cells, and central zone of necrosis; hematoxylin and eosin; reduced slightly from mag. × 50. (*b*) Healed granuloma consisting of dense fibrous tissue with few fibroblasts and central area of calcification; hematoxylin and eosin; reduced slightly from mag. × 70.

the usual markings were indistinct, but multiple irregular pinpoint light areas measuring up to 1 mm. in diameter were scattered over the surface. The liver was likewise diffusely enlarged, weighing 2830 gm., and its markings were indistinct on section. The remainder of the intra-abdominal organs appeared normal.

The kidneys weighed 170 and 175 gm., respectively, and had finely granular reddish surfaces. On section, the markings were distinct, and many reddish pinpoint spots were noted in the cortex.

Examination of the head revealed lateral occipital ventriculostomy wounds bilaterally. In the dura beneath the ventriculostomy sites were puncture wounds through which small nubbins of hemorrhagic brain protruded; otherwise the dura was intact. On external examination of the brain there were noted three vertically oval yellow softened areas on the left cerebral hemisphere, one over Broca's area, measuring 4.5 by 1.5 cm.; one over the anterior parietal area, measuring 2.5 by 1 cm., and one measuring 2 by 1.5 cm. in the lateral anterosuperior occipital area close to the ventriculostomy wound. A smaller, similar area measuring 0.5 by 0.5 cm. was present in the right occipital lobe beneath the right ventriculostomy wound.

On coronal sections of the brain the softened yellow areas on the cortex, mentioned above, continued as wedge-shaped yellow areas deeply into the brain, the anterior one extending into the internal capsule and the parietal one extending to a depth of 3.5 cm., while the left occipital one extended broadly to the posterior horn of the left lateral ventricle but did not communicate with it. The yellow scar in the right occipital lobe was limited to the cortex. There was slight swelling of the left hemisphere, with a shift of the midline structures to the right. There was moderate atrophy of the gyri, particularly of the frontal lobes, and there was moderate dilatation of the ventricles. The cerebrospinal fluid was clear.

The spinal cord was removed by the anterior route. The vertebrae were osteoporotic and markedly cellular, and the marrow of the bodies of the fifth lumbar and first sacral vertebrae was white. On exposure of the nerve roots a small amount of purulent material was found in and around the sheath of the first sacral root on the right.

Histologic Examination: Sections through the lesions in the cerebral hemispheres revealed areas of loss of normal architecture and replacement by large collections of swollen gitter cells containing

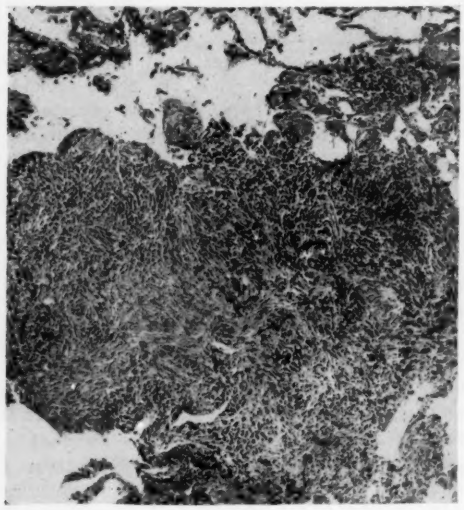


Fig. 3.—Typical nodule in the lung, consisting of dense fibrous tissue that contains irregular doubly refractile material and black pigment; the appearance is consistent with that of anthracosilicosis. Hematoxylin and eosin; reduced slightly from mag. × 65.

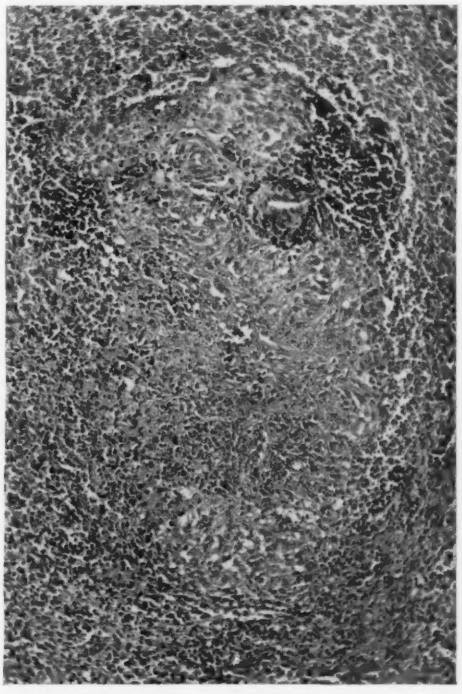
lipoid material; these cells surrounded areas of amorphous granular material with the outline of brain tissue. The gitter cells were sometimes free, but often they were enmeshed in a latticework of irregular fibrosed capillaries. Frequently among them, and also in the amorphous brain tissue, there were calcified neurons and glial cells and fine dust-like calcified material (Fig. 1). The blood vessels in the meninges, although usually showing only a moderate thickening of their walls, sometimes showed, in the areas of maximal degeneration, dense extensive endothelial and fibroblastic proliferation leading to partial and sometimes complete occlusion and even to central calcification. Surrounding the cystic areas the abutting white matter was filled with numerous small cavities, decreasing in number away from the cystic area. In the white matter surrounding the cavities there were hypertrophied gemistocytic astrocytes, which were more numerous around the cystic area. Perivascular lymphocytes were occasionally found in the surrounding white matter and frequently at quite some distance, and these were sometimes associated with a breakdown of the immediately surrounding myelin and the presence of gitter cells. In addition to the gross lesions, an occasional small focus of similar nature, usually limited to the cortex, was found elsewhere in the brain. In sections of the medulla and spinal cord there was evidence of partial degeneration of the left pyramidal tract.

Section of the root of the right first sacral nerve revealed two granulomas in the connective tissue surrounding the nerve fibers. One consisted of an outer layer of dense collagen within which was a narrow zone of cellular reaction of lymphocytes, plasma cells, and macrophages and a narrow ring of epithelioid cells. The center of the lesion was a mass of amorphous material with a slight amount of nuclear debris (Fig. 2*a*). The other had a similar outline but consisted of a small irregular rim of connective tissue surrounding a large mass of amorphous material, the center being calcified (Fig. 2*b*). These two lesions were the only ones that resembled specifically those seen in the biopsy specimens.

In sections of the lungs, numerous nodules consisting of masses of large epithelioid cells that contained brown and black granular pigment and occasionally doubly refractive bodies were found perivascularly and along the septa. These were occasionally encapsulated by fibroblasts, but they usually fused into the neighboring thickened alveolar walls (Fig 3). A moderate amount of precipitated protein was present in the alveoli. Sections of the myocardium of the posterior base of the left ventricle showed replacement of portions of the myocardium by dense fibrous tissue and hypertrophy of the neighboring myocardial fibers.

Microscopic examination of the liver showed dilatation of the sinusoids, some containing multinucleated cells; diffuse granularity of the hepatic

Fig. 4.—Proliferative reaction in the spleen with large numbers of pale mononuclear cells and central area of neutrophiles. Hematoxylin and eosin; × 80.



cells, and infiltration of the periportal spaces with lymphocytes, macrophages, and occasional neutrophiles. The sinusoids of the spleen contained large numbers of myelopoietic cells and occasional megakaryocytes. In addition, around some of the blood vessels there were large masses of histiocytes, occasionally with broken-down centers containing neutrophiles (Fig. 4). The centers of many of the Malpighian corpuscles contained irregular hyalinized strands.

The histologic sections of the kidneys revealed an extensive glomerular reaction. Most of the glomeruli had an extensive endothelial and epithelial proliferative reaction, with partial occlusion of the glomerular loops and the formation of crescents. In a few glomeruli there was a striking extensive infiltration by polymorphonuclear leucocytes which filled the glomerular capsule and spilled over into the neighboring connective tissue and tubules (Fig 5). Such purulent reactions were diffusely intermingled within the cortex and were not anatomically related in any way. The tubular epithelium was swollen, with irregular nuclei, and many tubules contained casts and occasionally leucocytes.

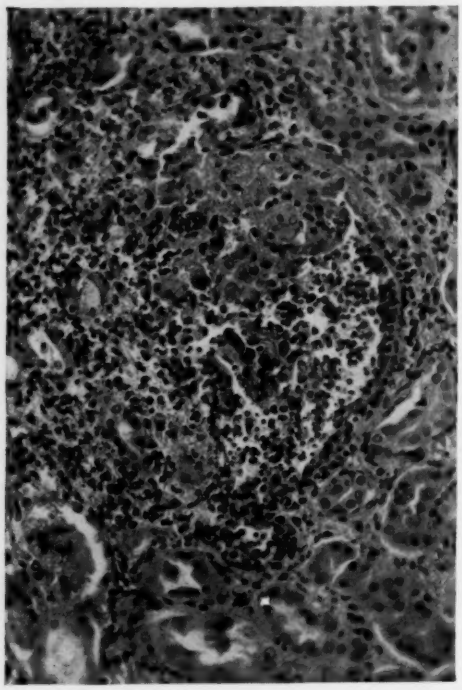


Fig. 5.—Acute lesion in the kidney. A glomerulus has been partially destroyed, with numerous neutrophiles filling part of Bowman's capsule and spilling out into the surrounding tubules.

Sections of the bone marrow showed a "monotonous" picture of cells of the early myeloid series, and there were large numbers of immature and degenerating megakaryocytes. The normal islands of erythropoiesis and myelopoiesis interspersed with fat were missing.

Histologic Examination of Biopsy Specimens.—Biopsy specimens had been taken from the skin and subcutaneous tissue of the right thigh 1 day after admission, from the left side of the neck and from the axilla 1 week later, from the right forearm 18 days after admission, and from the right thigh 28 days after admission. Each specimen revealed a picture, more or less distinct, of an infectious granuloma present in the subcutaneous tissue. The outer layer of the granuloma consisted of varying amounts of collagenous fibers. Within was a zone of cellular infiltration, primarily of lymphocytes and young fibroblasts, with varying admixtures of plasma cells and macrophages. New capillaries with variably thickened walls ran throughout this layer. Occasionally there was diffuse polymorphonuclear leucocytic infiltration. More centrally placed was a zone of pronounced cellular proliferation of epithelioid cells, which usually appeared in whorls but sometimes in palisades. They frequently formed rather large lobulated masses, and occasionally they made up the central portion of the granuloma. Usually the cells were long and thin, although in some areas they were rounded and vacuolated. Langhans-type giant cells were intermixed with these epithelioid cells, oftenest in the outer layer. The central area usually consisted of necrotic amorphous tissue debris with greater or lesser numbers of well-preserved or sometimes degenerating polymorphonuclear leucocytes.

Special stains for micro-organisms, including the periodic acid-Schiff stain, were unsuccessful in demonstrating bacteria or fungi.

COMMENT

Clinical Aspects.—Sporotrichosis is of relatively infrequent occurrence. The etiologic organism is a fungus, S. schenckii, which exists parasitically on many plants and timbers and is fairly widespread throughout the Mississippi Valley. However, cases have been reported from many different areas of the United States and from other areas of the world, and many of them have been reported in the form of unusual cases.[18] The portal of entry in man is a site of trauma to the skin. This feature is so characteristic that sporotrichosis has been considered an occupational disease.‡

‡ References 7 and 9.

The usual clinical picture of sporotrichosis is that of the localized lymphangitic form, with a nodule or ulcer at the site of trauma on an extremity.[5] This nodule or ulcer is followed by nodular lesions along the line of lymphatics of the extremity. These lesions usually break down and ulcerate if no therapy is given. It is rare for sporotrichosis to involve the viscera and be systemic in character. Extracutaneous sporotrichosis is often secondary to neglected cutaneous manifestations of the disease.[16]

Bacteriologic Aspects.—The strain of S. schenckii isolated from this patient conformed in all respects to the cultural features clearly described by Conant and co-workers.[5] Growth began to appear on the third day at 37 C, the colonies being in the yeast phase on enriched fresh-meat-infusion blood agar. The colonies were moist, smooth, and white, and when transferred to Sabouraud's agar at room temperature they developed in five days as flat grayish-white filamentous colonies which soon darkened to gray and finally became black, wrinkled, and leathery. The filaments were 2μ or 3μ wide, septate, and branching and developed lateral conidiophores on the tips of which were clusters of oval or pyriform conidia 2μ to 4μ long. The clusters contained from two to six conidia. Occasionally the conidiophore contained a solitary conidium. Some of the conidia were borne on very short stalks and were essentially sessile in their relation to the hyphae. The cells in the yeast phase were spherical, oval or pyriform and measured up to 6μ in length. The buds were attached to the parent cells by means of a very narrow constriction. Many cells had two or three buds, which at first suggested the possibility of Blastomyces brasiliensis. However, the parent cells were smaller than Blastomyces and did not have the thick walls of the latter. The transformation to the filamentous form with clusters of conidia and a black matted leathery growth without aerial mycelium ruled out Blastomyces.

It is important to note in this instance that there were only a few colonies of Sporotrichum noted per plate; no other organism was isolated from the biopsy specimen. From the gross and histologic appearance of the specimen one would have expected many organisms to be present. This paucity of organisms might well explain the failure of cultures from the previous biopsy specimens, which apparently did not include the center of the lesions. The following facts indicate that the colonies of Sporotrichum were not contaminants: 1. Sporotrichum has never been recognized as a contaminant in our laboratory. 2. The lesion from which the organisms were isolated was a subcutaneous nodule which was surgically excised and sent directly in a sterile container to the bacteriology laboratory. 3. No other organisms were present in the cultures made from the lesion. 4. The remaining subcutaneous nodules on the left arm rapidly disappeared under treatment with 2-hydroxystilbamidine.

At necropsy extensive bacteriologic examination was made of the kidneys, brain, sternal marrow, spleen, lungs, right sacral nerve, hilar lymph nodes, peripancreatic lymph nodes, choroid plexus, liver, and subcutaneous tissue from the left arm at the site of the nodules that were observed before the start of treatment with 2-hydroxystilbamidine. Particular efforts were made to isolate Sporotrichum and other fungi, as well as Brucella, tubercle bacilli, and the common pyogens. Mice were also inoculated intraperitoneally and intracranially, especially to isolate Toxoplasma. Except for an occasional contaminant, no organism was isolated from the necropsy material.

Attention should be called to the importance of careful studies relative to the identification of organisms. In 1927 Forbus [8] reviewed the cases of so-called pulmonary sporotrichosis which had been reported up to that time and pointed out that none was acceptable as a bona fide case. Other cases, some of which have been reported since then, lack proof that the offending organism was S. schenckii.

In the case described by Forbus,[8] as he indicated, the disease was probably not due to S. schenckii. The large filaments present in the lesions were larger than the hyphae of

Sporotrichum. Furthermore, Sporotrichum does not grow in the tissue as filaments. The case described by Warfield [24] was definitely not typical of sporotrichosis, and the organism isolated had features quite different from those of Sporotrichum, as shown by the description: "The columella, seen after the discharge of the spores, projects in a spherical body from the funnel shaped, expanding end of the supporting hyphae." The case described by King [12] also had features quite different from the usual case of sporotrichosis, especially the feature of failure to respond to iodide therapy. The photomicrographs indicate definitely that the organism isolated in his case was not S. schenckii, and this fact probably explains the comment that "exact classification of the organism has not been attempted."

The cases reviewed by Collins [3] and by Hyslop and his colleagues [11] may also not represent infections by typical S. schenckii. In the case reported by Collins the histologic reaction and the cultural features were atypical of those usually associated with sporotrichosis. Numerous intracellular organisms were found in the macrophages of the skin lesions, liver, spleen, and bone marrow. The photomicrograph shows oval intracellular encapsulated organisms quite suggestive of Histoplasma. They failed to grow on Sabouraud's or fresh-meat-infusion agar at 37 C, which would be unusual for Sporotrichum but common for Histoplasma. The case reported by Hyslop and co-workers [11] does not seem to represent sporotrichosis. Culture of the lesions gave negative results. The diagnosis apparently was made by finding "sporotrichia spores and mycelial forms" in the spinal fluid. It is rare to find mycelia of Sporotrichum in the tissue lesions.

Pathologic Aspects.—The histopathologic findings in our case were indicative of several processes. The lesions of the nervous system appeared to be directly related to sporotrichosis—definitely so in the root of the first sacral nerve, where the lesion was that of a healing granuloma, and probably so in the cerebral cortex. In the latter area, although the lesions histologically were a variant of the process of infarction, they were not lesions of acute vascular insufficiency but rather those of gradual insufficiency, such as follows endarteritis and such as is sometimes seen in cases of healed tuberculous meningitis with endarteritis.

Whether the lesions of acute polymorphonuclear reaction in the glomeruli and the areas of histiocytic proliferation with necrosis in the spleen were a direct effect of sporotrichosis cannot be determined. As in the other lesions, no organisms were visible, but these organisms are rarely found in tissue, and in our case they were not seen in the biopsy specimens even when cultures proved their presence. The reaction in the bone marrow, liver, and sinusoids of the spleen appears to have been part of the general reaction to the infection and does not appear to have changed greatly from that of the early lesions seen in the tissue removed at puncture biopsy.

The diffuse subacute glomerulonephritis could have been an allergic reaction and probably was related to the allergic manifestations that developed coincident with 2-hydroxystilbamidine therapy.

Finally, the silicosis-like lesions in the lungs and the lesions in the heart appear to have considerably antedated the immediate disease, and they probably played only a minor role in the reaction to the infection.

Comparison of the granulomatous reaction in the biopsy specimens with that in the nerve roots and brain discloses that in the biopsy specimens there was a varying amount of peripheral fibroblastic reaction but primarily there was an active endothelial proliferation with central necrosis and an acute inflammatory reaction. In the necropsy material, the two granulomas along the nerve root were quiescent, while those in the brain were definitely old and nonprogressive. Thus, no specific evidence of active sporotrichosis was found at the time of necropsy. Death appeared to have been due primarily to renal insufficiency and pulmonary edema.

Animal Studies.—Preliminary in vitro and in vivo studies in mice have been carried out with Sporotrichum. Three strains of S. schenckii, including the strain isolated in the

present case, were tested for their sensitivity to 2-hydroxystilbamidine dissolved in Sabouraud's dextrose agar and blood agar. All three strains were inhibited by 37.5γ to 250γ of this drug per cubic centimeter of medium. The in vivo studies to date have consisted of the observation of a series of 24 mice. Sixteen mice were given intraperitoneal inoculations of a suspension of the strain of Sporotrichum isolated from our patient; the other eight mice constituted drug controls. Treatment of eight of the inoculated mice was begun 48 hours after inoculation. One milligram of 2-hydroxystilbamidine was injected intraperitoneally every day for 14 days. Tissues of both the treated and untreated mice were examined by means of slide preparations and by culture after the mice had died from the infection or had been killed.

The preliminary data indicate that 2-hydroxystilbamidine may exert a suppressive effect on sporotrichosis under the conditions of the experiment. Further in vivo studies with a larger series of mice treated with 2-hydroxystilbamidine are now in progress and will be reported on later.

Biochemical Aspects.§—At necropsy, unembalmed specimens of the liver and brain were deep-frozen until they could be analyzed for 2-hydroxystilbamidine and iodine. The fluorophotometric method of Lieben and Snapper [18] was used for determination of 2-hydroxystilbamidine. The liver and brain tissues contained 55 mg. and 2 mg. of 2-hydroxystilbamidine, respectively, per 100 gm. of wet tissue; the corresponding values for a control patient who had not been given 2-hydroxystilbamidine were 2 mg. for the liver and 0 mg. for the brain. The iodide content of the liver and brain tissues was 7.2 and 2.6 mg. per 100 gm. of wet tissue, respectively.

The fluorophotometric determination of 2-hydroxystilbamidine in tissues allows for only a rough estimation of the diamidine present. Although the determinations were done two months after 2-hydroxystilbamidine therapy had been discontinued, significant amounts of the drug were found in the liver.

One can only say that, on the basis of the determinations mentioned above, heavy traces of 2-hydroxystilbamidine probably appeared in the brain. Marked traces of the diamidine have been found in the liver and the adrenals for as long as three years after cessation of treatment.[19]

Therapeutic Aspects.—Iodides have been considered almost a specific for the therapy of sporotrichosis.[5] This is especially so in treatment of the localized lymphatic form of the disease. The lesions usually clear up in several weeks to several months. When there has been visceral involvement, the iodides have not been so successful in therapy. The mechanism by which these salts are effective is not known. Although they are curative, it is known that Sporotrichum thrives well on an agar medium containing potassium iodide in a concentration of 10%. Iodides do not prevent experimental sporotrichosis in the rat, but infected rats can be cured with them.[16]

Recently, the aromatic diamidines have been investigated for their antifungal properties.‖ Two of these preparations, stilbamidine and 2-hydroxystilbamidine, have been reported to be of curative value in blastomycosis, leishmaniasis, disseminated coccidioidomycosis, and localized histoplasmosis.¶ Stilbamidine has been reported to be successful in therapy of the localized lymphatic form of sporotrichosis.[10]

2-Hydroxystilbamidine occurs as odorless small yellow crystals or as a yellow crystallized powder. It is stable in air but undergoes slow decomposition through hydrolysis of the amidine groups, especially when exposed to light. It is much more stable than stilbamidine. It is freely soluble in water or dextrose solution. The daily dose is usually 225 mg. given intravenously; in our case it was prepared freshly each day just before administration. This amount should be given slowly

§ Drs. M. H. Power and W. F. McGuckin, of the Section of Biochemistry, provided the data reported on the tissue studies.

‖ References 2, 6, 17, and 21.

¶ References 4, 15, and 22.

over a period of 45 to 60 minutes. As much as 23 gm. has been given without evidence of toxicity.[15] Trigeminal neuropathy has not been reported, as it has with stilbamidine. The drug gets into the liver, kidneys, and adrenals in large amounts and into the lungs and spleen to a lesser extent. It also gets into the cytoplasm and nuclei of brain cells in substantial amounts. Once in the tissue, it remains there for many months.[19]

2-Hydroxystilbamidine was given to our patient for the following reasons: Systemic sporotrichosis is often fatal even when treated with iodides; the two reported patients who were said to have sporotrichosis of the central nervous system had not responded to treatment with iodides; 2-hydroxystilbamidine has been considered a drug of low toxicity, and, finally, experimental evidence exists that the drug penetrates into the cytoplasm and nuclei of brain cells.[20]

The use of 2-hydroxystilbamidine in our patient appeared to have been accompanied by definite objective improvement. The neurologic aspects were improved, and the subcutaneous nodules almost completely disappeared during the first two weeks of treatment.

The acquired allergic sensitivity that developed in this patient is the first such reaction to be reported, to our knowledge. Had it not occurred, therapy with this drug probably would have been continued for a period of 50 to 60 days or more, depending on the clinical course of the disease. In view of the unsatisfactory therapeutic results with iodides in most cases of systemic sporotrichosis and in view of the fact that 2-hydroxystilbamidine had caused fairly rapid resolution of the subcutaneous nodules of sporotrichosis in one case, we were hopeful that 2-hydroxystilbamidine would prove curative in our case. That this did not occur may have been the result of our inability to give as long a course of therapy as seemed indicated because of the allergic sensitivity reaction. Minor toxicity from 2-hydroxystilbamidine has been reported when it has been given too rapidly intravenously. This reaction has consisted of generalized pruritus, weakness, dizziness, pallor, and tachycardia.

The improvement that occurred in our patient after a month of chemotherapy and the failure to culture this organism from the many tissue specimens obtained at necropsy, together with the evidence of healing lesions and the evidence of our preliminary in vitro and in vivo studies that 2-hydroxystilbamidine has a suppressive effect on sporotrichosis in mice caused by this particular strain of S. schenckii, all lend some support to the idea that this drug may be of curative value in systemic sporotrichosis. Further clinical and experimental trials seem indicated.

SUMMARY

An unusual case of widespread systemic (visceral) sporotrichosis together with involvement of the central nervous system is reported. Clinical and laboratory experiences with 2-hydroxystilbamidine in the treatment of this patient are described. The development of severe allergic sensitivity precluded the further use of this drug after a month of therapy. Necropsy revealed healing lesions of sporotrichosis. Death was apparently due to renal insufficiency coincident with the drug therapy.

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Thrombophlebitis, Blood Coagulation, and Pancreatic Disease

A Study of the Pancreatic Secretion in Patients with Thrombophlebitis

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The association of pancreatic cancer and recurring thrombophlebitis was first recorded by Trousseau.[1] In 1934, Sproul,[2] from a careful and extensive study of postmortem material, stressed the unusually high frequency of thrombophlebitis in malignant diseases of the body and tail of the pancreas. This finding has been corroborated by the investigations of Kenny [3] and others,* but the pathogenesis of the relationship has remained obscure. The most commonly suggested etiological mechanism has related the thrombophlebitis to alterations in blood coagulation.

Changes in the blood coagulation mechanism have been noted by many observers, usually in connection with studies of experimental and clinical pancreatitis.† Blood coagulation alterations have also been recorded in patients with pancreatic cancer and have been stressed recently by Shingleton [8] and Innerfield,[9] who introduced laboratory diagnostic procedures based upon them. Shingleton, using his paritol blood coagulation test technique, noted that an increased blood clotting reaction could be induced by neostigmine (Prostigmin) injection in patients with pancreatitis and pancreatic cancer. Innerfield reported increased antithrombin titers associated with acute pancreatitis and pancreatic malignant disease. Both phenomena were presumed to result from abnormally increased blood trypsin levels.

If hypertrypsinemia and the consequent alteration of blood coagulability are causative factors in the thrombophlebitis of pancreatic cancer, one would expect thrombophlebitis to occur in more constant association with pancreatic inflammatory disease, in which hypertrypsinemia is even commoner. Such a relationship has not been noted clinically.

The present study is the report of an investigation of the external pancreatic secretion, the serum amylase concentration, and the antithrombin titer in patients with thrombophlebitis.

METHODS

The patients studied all had actively persistent or recurrent thrombophlebitis. Subjects with traumatic, postoperative, postinfusion, or varicose phlebitis were excluded from this investigation. The patients were tested in the fasting state. Blood serum was drawn for amylase and antithrombin determinations. A double-lumened gastroduodenal tube was positioned fluoroscopically, and a secretin test was performed with the standard intravenous dosage of 1.0 clinical units per kilogram of secretin and a collection period of 80 minutes.

Blood amylase and antithrombin titers were studied to determine the presence of pancreatic hyperenzymasemia. The antithrombin titer, in addition, reflects alterations in the blood coagulation. The pancreatic response to secretin serves to define the state of pancreatic function in these patients. The normal range of blood amylase in this labora-

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The Secretin used in this study was donated by Dr. James B. Hammond, of Eli Lilly & Company, Indianapolis.

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* References 4 and 5.

† References 6 and 7.

tory is below 200 mg. per 100 cc. The antithrombin titers were performed according to the method of Innerfield and were interpreted according to his criteria.[9] The normal ranges for the secretin test responses were derived from a statistical study of the data of normal patients.[10] The critical values are as follows: volume, 2.0 or more ml/kg.; for maximum bicarbonate concentration, 90 or more mEq/L.; total enzyme secretion, 6.0 or more units of amylase/kg.

pancreatic secretion, the blood amylase level, and/or the antithrombin titers (Cases 1, 2, 6, 9, 20-23, and 25). Of these, three were explored and were shown to have pancreatic cancer (Cases 19 and 25) and chronic pancreatitis with pseudocyst (Case 23). Two patients (Cases 1 and 9) are known alcoholics, and, though neither presented a

Secretin Test Responses, Blood Amylase Concentration, and Antithrombin Titer Data of 33 Patients with Thrombophlebitis

Diagnosis	Secretin Test Data: Total Volume, Ml./Kg.	Secretin Test Data: Maximum HCO_3 Conc., mEq./L.	Secretin Test Data: Total Amylase, Units/Kg.	Blood Amylase, Mg./100 Cc.	Antithrombin Titer
1. Thrombophlebitis, alcoholism	2.6	79 *	8.8	482 *	Normal
2. Thrombophlebitis, duodenal ulcer	2.3	40 *	6.2	186	Normal
3. Thrombophlebitis	2.0	123	16.5	16	Normal
4. Thrombophlebitis, diabetes	2.8	107	7.3	127	Normal
5. Thrombophlebitis	2.2	100	7.0	169	Normal
6. Thrombophlebitis, biliary cirrhosis	2.4	108	4.8 *	105	High *
7. Recurring thrombophlebitis, postchol. synd.	3.1	122	16.4	176	Normal
8. Rec. thrombophlebitis, chr. ulcerative col.	2.2	98	9.5	130	Normal
9. Recurring thrombophlebitis, ? alcoholism	0.8 *	64 *	3.0 *	164	Normal
10. Recurring thrombophlebitis, diabetes	4.4	112	18.1	42	Normal
11. Recurring thrombophlebitis	2.1	110	14.5	40	Normal
12. Recurring thrombophlebitis, sprue	5.1	96	16.3	49	Normal
13. Recurring thrombophleb., postchol. synd.	2.5	121	8.3	38	Normal
14. Rec. thrombophlebitis, pulmonary embolism	2.3	97	11.5	76	Normal
15. Recurring thrombophlebitis, pulm. embolism	2.0	110	11.4	115	Normal
16. Rec. thrombophleb., postchol. synd., pulmonary embolism	3.0	119	27.0	76	Normal
17. Rec. thrombophleb., abd. pain et?	3.3	126	14.2	37	Normal
18. Rec. thrombophleb., diabetes, abd. pain et?	2.6	134	16.2	125	Normal
19. Rec. thrombophleb., diabetes, ca. head panc.†	1.2 *	33 *	0.8 *	42	Normal
20. Rec. idiopathic bilateral thrombophlebitis	2.3	72 *	4.7 *	168	High *
21. Recurring thrombophlebitis, diabetes	2.5	61 *	13.7	33	Normal
22. Migratory phleb., chr. pancreatitis, pseudocyst †	2.9	63 *	10.4	475 *	Normal
23. Mig. thrombophleb., pulm. embolism	2.7	124	23.5	85	Normal
24. Migratory thrombophlebitis	2.3	98	6.5	44	Normal
25. Mig. thrombophleb., ca. body pancreas †	1.8 *	112	14.4	74	High *
26. Mig. phlebitis, postcholecystectomy synd.	2.2	93	18.8	82	Normal
27. Rec. migratory thrombophlebitis	2.2	129	23.8	97	Normal
28. Migratory thrombophlebitis	2.3	127	17.5	94	Normal
29. Mig. thrombophleb., atypical Buerger's dis.	2.3	90	10.3	53	Normal
30. Thromboangiitis obliterans	3.0	132	24.0	56	Normal
31. Thromboangiitis obliterans	2.8	135	27.2	74	Normal
32. Thromboang. oblit., hiatus hernia	3.9	105	9.8	152	Normal
33. Thromboang. oblit., duodenal polyp	3.6	118	29.2	117	Normal
Lower limit of normal range	2.0	90	6.0	200	

* Abnormal.
† Explored.

RESULTS

The results of the investigations in 33 patients are presented in the Table. The patients are grouped according to diagnoses of thrombophlebitis (6), recurrent thrombophlebitis (15), migratory phlebitis (7), and thromboangiitis obliterans (5).

Among the 33 patients studied, there were 9 patients who showed abnormalities in the definite history of previous acute pancreatitis, the association of alcoholism and abnormal pancreatic response to secretin is strong evidence in favor of a diagnosis of chronic pancreatitis. In two patients (Cases 6 and 20) abnormalities of the secretin test suggesting pancreatic inflammatory disease were associated with elevations of the antithrombin titer. In the remaining two patients (Cases

2 and 21), there is no other evidence to confirm a diagnosis of chronic pancreatitis.

The alterations observed in the secretin test were low volume response in three instances (Cases 9, 19, and 25). Two of these patients were proved to have pancreatic cancer. In five patients the abnormality of secretion was a decrease in bicarbonate (Cases 1, 2, and 20-23), and in the remaining patient (Case 6) there was an isolated enzyme deficiency. Diminished bicarbonate and enzyme secretion is indicative of pancreatic inflammatory disease; diminished volume flow is diagnostic of pancreatic cancer.

Two patients had elevated blood amylase levels, 482 mg. and 475 mg. per 100 cc., in Cases 1 and 23, respectively. The latter patient had proved chronic pancreatitis; the former patient, an alcoholic, has a presumed case of chronic pancreatitis. The remaining blood amylase determinations were normal.

Three patients displayed abnormally high antithrombin titers. One of these (Case 25) was the patient with pancreatic cancer. The other two (Cases 6 and 20) had abnormal secretin tests. The antithrombin titer was normal in all other patients, including the two with elevated blood amylase. In all instances in which the blood amylase or the antithrombin titer was abnormal the secretin test response was also abnormal.

COMMENT

The finding of 9 patients with abnormal pancreatic secretion in a group of 33 patients with peripheral thrombophlebitis serves to emphasize the clinical association of thrombophlebitis and pancreatic disease. Moreover, the fact that in seven of these patients the lesion is pancreatic inflammation rather than pancreatic neoplasm certainly has definite implications concerning the mechanism by which the phlebitis is produced. The pathogenesis of phlebitis in patients with pancreatic cancer has been extensively discussed by previous investigators. Among the theories offered to explain this relationship have been the following:

1. Alteration in the blood coagulation mechanism due to ‡
   - (*a*) Disturbance in liver function
   - (*b*) Disturbance in protein digestion
   - (*c*) Increased secretion of pancreatic enzymes into the blood §
     - (1) Hyperlipasemia and its effect on blood cephalin
     - (2) Hypertrypsinemia and its effect on coagulation time
2. Secretion of abnormal substances by the tumor into the blood ||
   - (*a*) Thrombocytosis ¶
   - (*b*) Mucin #
3. Increase in venous pressure due to *
   - (*a*) pressure of the tumor on venous channels
   - (*b*) cachexia, dehydration, and congestive heart failure
4. Metastases of cancer cells to venous channels with irritation of the epithelium by secretion of trypsin.[2]

The demonstration of pancreatic inflammatory disease in association with peripheral phlebitis in this series and in the investigation of others † is strongly in favor of the first etiological factor mentioned, namely, alteration in the blood coagulability. The precise effect of pancreatic secretion and pancreatic disease on blood coagulation, however, has not been completely elucidated.[16]

Decreases in the blood coagulation time of patients with pancreatic cancer have been reported by a number of observers.‡ The opposite, increase in coagulation time, has been noted in patients with acute and chronic pancreatitis.§ On the other hand, experimentally, extirpation of the pancreas [24] or external diversion of the pancreatic juice

‡ References 2 and 4.
§ References 44-47.
|| References 12 and 13.
¶ References 5 and 14.
# References 3, 4, and 15.
* References 2 and 4.
† References 6 and 7.
‡ References 17-20.
§ References 16 and 21-23.

as well as ligation of the main pancreatic duct || is followed by an increase in the blood coagulation time. Boldyreff [25] demonstrated prolongation of the coagulation time in dogs during periods of pancreatic hypersecretion and decreases in the coagulation time during pancreatic hyposecretion. Lasher and McCabe [7] reported prolongation of both the prothrombin and the coagulation time in experimental pancreatitis and made similar observations in patients. Shinowara [29] described an increase in the fibrinogen content and the thromboplastin plasma component concentration in experimental pancreatitis and in patients with acute pancreatitis or with exacerbations of chronic relapsing pancreatitis.

Along with these changes in blood coagulation factors there have been reports of alteration in the blood proteolytic activity in pancreatic disease. Rush and Clifton [30] have noted an increased titer of serum proteolytic activity, and Coffey [31] observed fall in the serum antiproteolytic titer in the acute phase of experimental as well as clinical pancreatitis.

These clinical and experimental observations of the behavior of the clotting time, the proteolytic activity, and the antiproteolytic titers have been correlated with the similar changes noted in the blood following the intravenous injection of trypsin into animals,¶ with the conclusion drawn that the alteration of blood coagulability in pancreatic disease is due to changes in the blood trypsin levels.# There is good evidence that high concentrations of pancreatic enzymes not only may be disseminated into the bloodstream,[44] the lymphatics,[45] and the body tissues as a result of hypersecretion of inflamed pancreatic tissue or obstructed pancreatic tissue but also may arise from functioning tumors of acinar tissue [46] and from their metastases even after removal of the primary neoplasm.[47]

There has been some difficulty in explaining the difference in the effect of trypsin on blood coagulation in vitro as compared with the observations in vivo. In vitro * small amounts of trypsin will accelerate coagulation and large amounts will completely inhibit coagulation. In vivo, very small amounts of trypsin [36] appear to inhibit the blood coagulation by a diminution in prothrombin, labile factor (ac-globulin), and fibrinogen, with prolongation of the bleeding and coagulation time. This effect is thought to be due to a selective digestion of specific coagulation factors and to the activation of a blood proteolytic enzyme system.[37] Innerfield,[9] using the antithrombin titer as a measure of the blood proteolytic activity directly and the blood trypsin level indirectly, has offered the hypothesis that the increase in the coagulation time in pancreatic cancer and acute pancreatitis is due to the hypertrypsinemia resulting from pancreatic duct obstruction. The increased coagulability (decreased coagulation time) in certain cases of chronic pancreatitis and pancreatic fibrocystic disease, then, reflects a hypotrypsinemia. This hypothesis appears to be supported by the clinical observations of the antithrombin titers in acute pancreatitis,[38] pancreatic cancer,[39] and pancreatic fibrosis.[40]

While Innerfield's hypothesis appears consistent with clinical and experimental data, it does not fully explain the venous thrombosis and thrombophlebitis of pancreatic disease.[16] If hypertrypsinemia is the cause of thrombophlebitis, a higher incidence of thrombophlebitis would be expected in carcinomas of the head than in cancers of the tail of the pancreas; if hypotrypsinemia is the cause of the thrombotic tendency, then the incidence of thrombophlebitis should be greater in chronic inflammatory disease and fibrocystic disease of the pancreas than in pancreatic tumor. Neither of these suppositions is in accordance with clinical experience; that there is a higher incidence of thrombophlebitis in cancers of the tail of the pancreas and that the incidence of thrombophlebitis is greater in pancreatic tumor are observed clinical facts.

|| References 24 and 28.

¶ References 8 and 32-34.

References 6, 8, 9, 16, and 30.

* References 32, 34, and 35.

Others,† impressed by the appearance of vascular thrombi and inflammatory reaction surrounding areas of trypsin administration, have postulated that hypertrypsinemia may produce the thrombophlebitis by favoring coagulation and by directly irritating venous endothelium. Such a theory, however, again cannot explain the increased occurrence of peripheral thrombophlebitis in conditions of the pancreas in which either hyposecretion or hypersecretion exist, viz., pancreatic cancer, acute pancreatitis, and chronic pancreatitis.

The study herein reported in no way answers the problems posed by the association of venous thrombosis and phlebitis in pancreatic disease. The findings merely emphasize that phlebitis, altered blood coagulation, and evidences of pancreatic hyperenzymasemia occur in pancreatic inflammatory disease as well as in pancreatic neoplasm.

SUMMARY AND CONCLUSIONS

A study is presented on the external pancreatic secretion following secretin, the blood amylase level, and the blood antithrombin titer in 33 patients with peripheral thrombophlebitis. Nine patients showed evidences of pancreatic disease. Of these, two had pancreatic cancers; the remaining seven patients had pancreatic inflammatory disease.

The association of altered blood coagulability and phlebothrombotic phenomena in patients with pancreatic disease is discussed. Although there is much evidence that this relationship is caused by an alteration in the blood trypsin level, no hypothesis has been offered which adequately explains the pathogenesis.

The occurrence of thrombophlebitis in pancreatic inflammatory disease as well as pancreatic neoplasm is noted and stressed.

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Agranulocytosis Associated with Administration of Chlorpromazine

Report of Three Cases with Description of Treatment and Recovery

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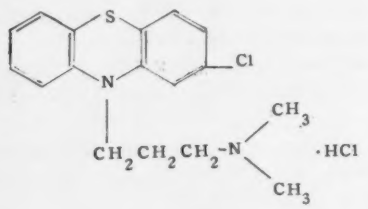
For more than 20 years, it has been recognized that aromatic organic compounds containing nitrogen atoms in certain linkages are capable of producing serious depression of leucocyte production and agranulocytosis; therefore, it is not surprising that after a period of extensive use of chlorpromazine, which is such an organic compound (Figure), this complication from the use of the drug should be encountered.



Chlorpromazine hydrochloride (10-[3-dimethylaminopropyl]-2-chlorphenothiazine hydrochloride).

It is not considered necessary to discuss the history of the recognition of agranulocytosis as a specific entity or the development of certain aspects of the treatment, which are covered adequately in the systems of medicine. Particular reference is made to the chapter on agranulocytosis in the Oxford Medicine, by Dameshek.

The patients who form the basis of this report were a part of the series of psychotic patients in treatment at Longview State Hospital, Cincinnati. The chlorpromazine was given for treatment of various psychotic states. At the time of this writing, more than 1000 patients have been treated with the drug. The present report deals with three patients who developed agranulocytosis under my care while receiving chlorpromazine for treatment of psychotic conditions.

Submitted for publication April 6, 1955.

From Longview State Hospital; Dr. E. A. Baber, Superintendent.

Chlorpromazine was furnished, as Thorazine, through the courtesy of Smith, Kline & French Laboratories.

CASE 1.—M. E. W., age 60, white woman, suffering from involution psychosis. Chlorpromazine treatment was started June 8, 1954, 50 mg. t. i. d.; June 16, this was increased to 100 mg. t. i. d. Her psychotic condition was markedly improved with continued treatment. On July 30, 1954, she was found to have fever (temperature of 104 F) and severe sore throat. There was immediate suspicion of the possibility of agranulocytosis, since this complication was expected from the use of the drug, although it had not previously been encountered or reported. It was found that the patient's white blood cells numbered only 2300 and the neutrophilic leucocytes were entirely absent. The blood count data, from onset to recovery, are presented in Table 1, with accompanying maximum daily temperatures. Treatment was as follows: penicillin was given daily from July 30 until August 16, 600,000 units twice daily intramuscularly. Beginning July 31, corticotropin was given in the following manner: 40 units intramuscularly in the gel form daily until Aug. 8, 1954, and, in addition, 20 units intravenously dissolved in 500 ml. of dextrose in saline on Aug. 2, Aug. 3, and Aug. 4. During the period when the patient's temperature was elevated, she received acetysalicylic acid, 10 grains (600 mg.) every four hours. At the time of recognition of the patient's complication, she was found to have an allergic type of dermatitis, chiefly urticarial, a fairly common complication of chlorpromazine treatment. One of the lesions on the dorsum of the right hand showed early necrotic change. This necrotic change progressed in a few days to a fairly large necrotic area, approximately 2 cm. in diameter. This sloughed out in the course of two

TABLE 1.—*Patient M. E. W.*

Date	Hgb.	RBC, Million	WBC	Neutrophiles	Eosinophiles	Basophiles	Lymphocytes	Monocytes	Maximum Daily Temperature, F *
4/30/54 (on admission)	14.5	4.7	6,100	..	..	..	..	..	.....
7/30/54	13	4.4	2,300	..	..	..	96	4	104
7/31/54	14	4.4	1,500	..	..	..	92	8	103.8
8/ 1/54	..	...	.....	..	..	..	..	..	101
8/ 2/54	..	...	1,300	..	..	..	100	..	102.8
8/ 3/54	..	...	2,100	5	..	..	90	5	101.8
8/ 4/54	..	...	2,700	19	..	..	77	4	101.6
8/ 5/54	..	...	1,900	29	..	..	63	8	100.2
8/ 6/54	..	...	3,400	36	..	6	57	6	99.8
8/ 7/54	..	...	4,400	31	3	..	66	..	99
8/ 8/54	..	...	.....	..	..	..	..	..	100
8/ 9/54	..	...	10,600	58	7	3	32	..	100
8/10/54	..	...	22,100	62	3	..	32	3	99.8
8/11/54	..	...	24,100	71	2	..	27	..	99.8
8/12/54	..	...	15,700	72	..	..	26	2	100
8/13/54	..	...	11,700	80	1	..	19	..	100.4
8/14/54	..	...	.....	..	..	..	..	..	99
8/15/54	..	...	.....	..	..	..	..	..	99
8/16/54	..	...	10,700	68	1	..	31	..	99
8/17/54	..	...	8,900	78	..	..	22	..	101
8/18/54	..	...	.....	..	..	..	..	..	99.4
8/19/54	..	...	7,600	58	1	..	41	..	99
8/20/54	..	...	.....	..	..	..	..	..	99.8
8/21/54	..	...	.....	..	..	..	..	..	98.6
8/24/54	..	...	14,100	59	..	..	41	..	.....
8/31/54	..	...	12,500	66	1	..	33	..	.....
9/ 2/54	..	...	20,600	72	1	..	26	1	.....
9/ 9/54	..	...	10,700	68	2	..	30	..	.....

* All temperatures were rectal.

weeks, and the area healed in about another month. For the general allergic dermatitis pyrilamine maleate (Neo-Antergan) 100 mg. was given every four hours beginning Aug. 2 and continuing to Aug. 16, when the dermatitis had entirely subsided. Patient's mental status, as well as the agranulocytosis, improved to the point of complete recovery, and she was subsequently able to leave the hospital.

CASE 2.—R. H., age 30, white woman, suffering from paranoid schizophrenia. Treatment with chlorpromazine was started Aug. 3, 1954, 50 mg. t. i. d.; Aug. 10, this was increased to 100 mg. t. i. d. On Sept. 16, patient was found to have high fever, a severe sore throat, extremely low white cell count, and a small necrotic lesion on the tip of the tongue. Patient had a mild cough as well. The chlorpromazine was immediately discontinued. The records of blood counts and maximum temperatures, from onset to recovery, are indicated in Table 2. The patient's temperature began to drop on the second day, but it increased again the following day, apparently as the result of pulmonary infection or resistance of at least some of the infection to penicillin. It was believed that she had bronchitis or early bronchopneumonia at this point. Treatment was carried out as follows: Penicillin, 800,000 units, was given intramuscularly every four hours the first day and twice daily from Sept. 17 to Sept. 24; 400,000 units was given intramuscularly daily from Sept. 25 to Oct. 9. Pyribenzamine, 50 mg., was given every four hours, even though there was no gross allergic manifestation, because of the experience with Case 1. Corticotropin gel, 40 units, was given intramuscularly daily from Sept. 16 to Sept. 24, and 20 units was given daily from Sept. 25 to Sept. 27. In addition, the patient was given 40 units intravenously in dextrose and salt solution daily from Sept. 17 to Sept. 20, inclusive. On Sept. 17, as the result of an overzealous intern's interest, she was given 500 cc. of whole blood; this was not repeated. Beginning Sept. 20, when the temperature rose a second time and there was evidence of a pulmonary infection, patient was given tetracycline, 500 mg. every four hours orally and 100 mg. intravenously. This treatment was continued for two days and then the tetracyline was given orally alone from Sept. 22 to Sept. 24. She recovered entirely from the pharyngeal and the pulmonary infections and improved mentally sufficiently to be able to leave the hospital in excellent condition. The necrotic lesion at the tip of the tongue healed with formation of a moderate scar.

CASE 3.—H. B., age 34, white woman, was a chronic psychotic patient admitted in 1931. Diagnosis was schizophrenia. Chlorpromazine was started Aug. 31, 1954, 50 mg. t. i. d.; this was increased to 100 mg. t. i. d. Sept. 8, 1954, and Sept. 16,

TABLE 2.—*Patient R. H.*

Date	Hgb.	RBC, Million	WBC	Neutrophiles	Eosinophiles	Lymphocytes	Monocytes	Maximum Daily Temperature, F *
6/25/54 (on admission)	13.5	4.6	8,900	..	..	..	..	.....
9/16/54	11	4.3	1,700	3	..	93	4	104
9/17/54 a. m.	11.5	4	350	9	..	85	6	104
9/17/54 p. m.	..	....	250	..	..	98	2	.....
9/18/54	12	4.2	720	13	..	87	..	101.6
9/19/54	..	....	.....	..	..	..	..	104
9/20/54	11.5	4.3	500	1	..	93	6	105.2
9/21/54	12	4.3	1,700	3	..	95	2	101.8
9/22/54	13	4.5	2,100	17	..	83	..	102.2
9/23/54	..	....	8,400	28	..	69	3	100.2
9/24/54	12	4.2	12,900	31	..	69	..	100.4
9/25/54	12	4.2	27,400	57	..	40	3	99.8
9/27/54	13.5	4.1	27,100	81	..	18	1	99.2
9/28/54	13.5	4.1	29,700	81	..	19	..	99.8
9/29/54	12.5	4.2	23,100	84	..	16	..	99
9/30/54	12	4.3	29,900	77	6	15	2	100
10/ 1/54	13	4.2	14,600	84	..	16	..	99.4
10/ 2/54	12.5	4.2	14,300	78	3	19	..	98.8
10/ 4/54	13	4.2	15,400	76	..	24	..	99.8
10/ 5/54	12.5	4.4	14,200	81	..	19	..	98.8
10/ 6/54	12.5	4.3	14,300	74	1	25	..	98.6
10/14/54	12	4.2	13,400	73	1	26	..	.....
2/ 4/55	10.5	3.3	8,600	62	6	31	2	.....

* All temperatures were rectal.

1954, it was increased to 200 mg. t. i. d. On Oct. 13, 1954, the patient was found to have temperature of 106 F in the evening. Chlorpromazine was immediately discontinued. On the morning of Oct. 14, she was found to have a not unexpected low white cell count, with almost absent neutrophilic cells. Blood cell counts and maximum daily temperatures are presented in Table 3. She had a sore throat with a necrotic lesion in the right side of the pharynx. X-rays of the chest showed early bronchopneumonia. Treatment was given as follows: Penicillin, 300,000 units twice daily Oct. 14; 800,000 units twice daily from Oct. 15 to Oct. 31, and 400,000 units twice daily Nov. 1 and Nov. 2. Tetracycline was given as follows: On Oct. 14, 100 mg. given intravenously, 500 mg. orally every four hours. The oral dose was continued daily every four hours until Oct. 21, when signs of the pulmonary infection had abated. While the temperature was elevated, the patient was given acetylsalicylic acid, 0.6 gm. every four hours. Corticotropin was given as follows: The gel form, 40 units intramuscularly twice daily on Oct. 14, 15, 16, 17, 18, 19, 20, and 21, and 40 units dissolved in dextrose and saline solution intravenously Oct. 14, 15, 16, and 17. The patient entirely recovered from the agranulocytosis and from the pharyngitis and pulmonary infection. Her mental status was moderately improved.

TABLE 3.—*Patient H. B.*

Date	Hgb.	RBC, Million	WBC	Neutrophiles	Eosinophiles	Lymphocytes	Monocytes	Maximum Daily Temperature, F *
10/13/54	..	...	.....	..	..	..	..	106
10/14/54	13	4.5	1,900	2	..	98	..	104
10/15/54	..	...	300	3	..	97	..	102
10/16/54	..	...	120	1	..	98	1	100.2
10/18/54	..	...	500	2	..	97	1	102
10/19/54	..	...	1,000	12	..	81	7	102.6
10/20/54	..	...	3,400	33	..	63	4	101.4
10/21/54	..	...	7,300	27	..	73	..	99.6
10/22/54	..	...	12,600	65	..	30	5	100.2
10/23/54	12	4.2	14,800	39	2	61	..	100.8
10/24/54	..	...	.....	..	..	..	..	100.2
10/25/54	..	...	17,500	78	..	20	..	100.8
10/26/54	..	...	17,200	76	..	24	..	100.2
10/27/54	..	...	16,300	71	3	26	..	100.8
10/28/54	14.5 (Platelets, 568,800)	4.8	18,900	69	2	29	..	100.4
10/29/54	..	...	13,500	17	..	83	..	100
10/30/54	..	...	12,900	31	..	69	..	100
11/ 5/54	..	...	10,500	73	1	26	..	99.6

* All temperatures were rectal.

COMMENT

The three patients whose clinical course is described showed clearly the classic characteristics of agranulocytosis: (1) severe sore throat, (2) absence of leucocytes of the granulocyte series in the acute stage of the condition, and (3) presence of a clearly defined necrotic lesion. The necrotic lesion is of particular interest in Case 1 because of its possible theoretic implications. This patient had an allergic type of dermatologic reaction to chlorpromazine. One of the urticarial lesions on the dorsum of the hand became necrotic, as in the Arthus phenomenon. The necrotic area, approximately 2 cm. in diameter, may represent a key to the destructive effect on leucocytes. The allergic humoral reaction may be synergistic with some product of the necrotic lesion to produce the specific leucotoxic effect.

Treatment of these patients in part followed the suggestion of Dameshek. Large doses of antibiotics were administered to combat the infection, to which it must be assumed the patients were rendered susceptible because of the absence of the granulocytic leucocytes. In addition, corticotropin was administered to produce stimulation of production of the neutrophilic granulocytes by the bone marrow.

The response of all the patients followed a consistent pattern. The initial level of white blood cells at the time of clinical recognition of the difficulty diminished for one or two days, apparently in spite of treatment, to the minimum level observed. Following this, the number of leucocytes at first slowly increased, then rapidly increased to a high level of leucocytosis, apparently "overshooting" the normal level. The maximum level observed (in Case 2) was 29,900. After the period of leucocytosis, the blood cell count returned to normal level, with some tendency to fluctuation. The period from minimum count to the normal level required eight, six, and five days, respectively, and the fluctuation at the higher than normal level persisted for a period of two or three weeks, with considerable variability. The leucocytosis following the severe leucopenia must be considered to reflect the intensity of the infection associated with the loss of cells of the granulocyte series initially and perhaps also the intensity of stimulation of the bone marrow produced by corticotropin under the specific conditions of this illness. Corticotropin in these patients may also be considered as a specific antiallergic agent.

Some mention should be made of the observation of leucopenia at levels closer to the normal range in patients receiving chlorpromazine. When moderate leucopenia was observed early in the course of the work with chlorpromazine, it was considered an indication for immediate termination of treatment. After experience in treating agranulocytosis had been gained, however, such mildly leucopenic patients were continued on treatment, with more frequent observation of the blood cell count, and were not found to develop agranulocytosis but were found merely to have fluctuations of white blood cell count between 3000 and 5000/cu. mm. It may well be that such patients represent the persons who normally have low white cell counts and do not represent reactions to chlorpromazine.

SUMMARY AND CONCLUSIONS

Case reports of three patients who suffered agranulocytosis as the result of administration of chlorpromazine are presented. The method of treatment carried out in these patients with regular and consistent beneficial results on the agranulocytosis is described. All three patients recovered from agranulocytosis, and two of the three improved sufficiently in their psychotic states from administration of chlorpromazine to be able to leave the state hospital. Leucopenia without agranulocytosis is discussed in relation to the treatment program with chlorpromazine. Certain theoretical clinical considerations are briefly discussed in relation to development of agranulocytosis.

NOTE.—Since the completion of this manuscript, the fourth patient suffering from agranulocytosis from the use of chlorpromazine has been encountered. This patient did not recover and died on the third day after recognition of the illness. This case will probably be reported in detail with autopsy findings in the future.

Carcinoid Tumors of the Gastrointestinal Tract

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Carcinoid tumors may arise anywhere in the gastrointestinal tract from the cardia to the rectum. They have also been reported in ectopic tissue of the gastrointestinal tract, as in dermoid cysts. Rarely, they are found in the bronchi, gall bladder, Meckel's diverticulum, nasal cavity, cervix, pancreas, neck, extrarectal region, testis, prostate, mesentery, and liver.

Carcinoid tumors of the gastrointestinal tract are comparatively rare lesions, although increasing numbers of cases are being reported with better understanding of the pathogenesis and pathology. Incidences ranging from 0.65% to 1.8% have been reported. Between 1947 and 1954, twenty-four cases of carcinoids of the gastrointestinal tract were encountered at the Ochsner Clinic. In addition, there was one carcinoid of the appendix seen in 1943. Our experience with these 25 cases will be reviewed and the literature on carcinoids discussed.

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HISTORY

Lubarsch [1] is generally credited with describing the first case of carcinoid in 1888, although six years earlier Berger * reported a case of appendiceal tumor which was believed by later authors to be a carcinoid. Lubarsch thought that his two cases were similar to a small polypoid tumor of the ileum involving the submucosal and muscularis layers and presenting an infiltrating alveolar structure described in 1867 by Langhans.[3] Lubarsch's two patients had small submucosal multiple tumors of the ileum. His description of carcinoids as columns or masses of cells and pseudoglandular formations cannot be improved upon today. Recognizing the tumor as distinctly different from carcinoma, he used the term "little carcinomata." He believed these probably arose from the crypts of Lieberkühn, as did Ransom,[4] who reported the first case with widespread metastases in 1890. Oberndorfer [5] was the first to insist that carcinoids belong in a separate group. He erroneously believed they were all benign and introduced the word carcinoid to distinguish them from malignant tumors.

PATHOGENESIS

Considerable investigation has been undertaken in an attempt to ascertain the site of origin of carcinoids. Several investigators, detecting their resemblance to basal-cell carcinoma of the skin, thought that they might be derived from the intestinal mucosa in a similar manner and called them basilomas or basal-cell carcinomas. They have been considered to represent embryonic remnants of the ductus omphalomes entericus. Other the-

* Berger, A., cited by Foreman.[2]

ories attribute their origin to pancreatic tissue, embryonic epithelial rests, Schwalbe's or Paneth's granular cells in the crypts of Lieberkühn, embryonic heterotopic tissue, cells of the celiac ganglia, Schmidt's cells in the crypts of Lieberkühn, cells of Auerbach's plexus, and the chromaffin granular cells in the crypts of Lieberkühn. In 1914 Gosset and Masson [6] demonstrated the argentaffin properties of certain cells near the bases of the crypts of Lieberkühn. Fourteen years later Masson [7] published his comprehensive study showing that carcinoid cell columns result from "proliferation of intranervous argentaffin cells of the neurocrine type." He explained that these cells migrate from the crypts of Lieberkühn to the nerves of the periglandular plexus. Continuing, he wrote, "They differentiate into various forms, cylindrical cells grouped in rosettes or vesicles, cells of ganglion type, of schwannian type, neurocrine cells." He believed that any autonomous proliferation of these cells will produce a carcinoid in the submucosa.

With the granular cells in the base of the crypts of Lieberkühn established as the site of origin for carcinoids, intensive study was done on these cells. Heidenhain [8] described the chromaffin reaction of certain cells of the gastric mucosa in 1870, and Schwalbe † first observed granular cells in the crypts of Lieberkühn. The ability of some cells in the crypts to take up particular dyes or colors in these granules was noted by Gosset and Masson,[6] among other investigators.

These cells are scattered among the mucous-secreting (goblet) cells lining the crypts of Lieberkühn (Fig. 1). They are occasionally found in the stomach but are commonest in the appendix and duodenum and relatively rare in the jejunum, ileum, and large intestine. There is some dispute regarding their function. Some believe they have an endocrine function like the pancreas, whereas others believe they simply supply ferments to the intestinal juice.

The cytoplasmic granules of many of these cells have a peculiar affinity for reducing silver salts. For this reason, these tumors are frequently called argentaffin tumors. However, not all carcinoid tumors have this silver-reduction ability. This is explained by all phases of differentiation of these cells. Popoff [10] showed that these cells in the basal layer of the crypts are differentiation cells which represent cytomorphosis of the mucous cells of the colon and small intestine or of the parietal cells of the stomach. The cell may undergo rejuvenation to become differentiated into a mucous cell, or it may remain undifferentiated.

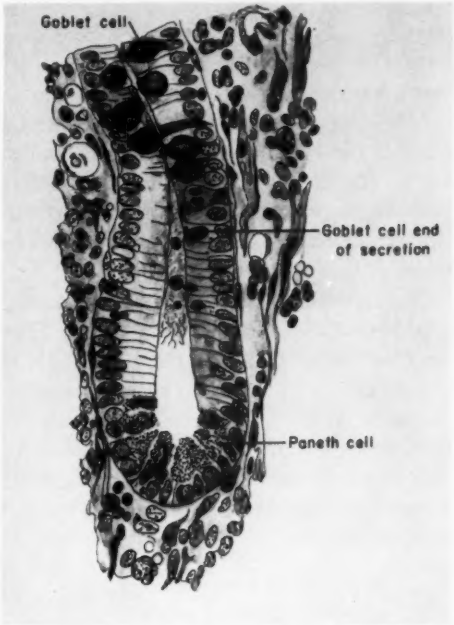

Fig. 1.—Crypt of Lieberkühn; × 380. (After Schaffer, in Maximow, A. W., and Bloom, W.: A Textbook of Histology, Philadelphia, W. B. Saunders Company, 1943, p. 409.)

In agreement with Popoff's observation that there are various phases of development, Erspamer ‡ described four cell types: (1) a typical cell having the granules and containing a chemical substance, enteramin; (2) a clear nonargentaphilic preenterochrome cell that has no granules; (3) a preenterochrome acidophile argentaphile cell that has acidophile granules which take up silver but contain no enteramin, so that they are unable to

† Schwalbe, C., cited by Cooke.[9]

‡ Erspamer, V., cited by Stout.[11]

reduce silver, and (4) the empty enterochrome cells which have granules that have been emptied of enteramin.

LOCATION

Carcinoids are rarely found in the stomach, duodenum, or jejunum. In an extensive search of the literature we were able to collect only 26 cases of carcinoids in the stomach, 24 in the duodenum, and 17 in the jejunum.

The commonest site of carcinoids reported in the literature is the appendix. These tumors are found in approximately 1.5% of all surgically removed appendices. Moreover, 90% of appendiceal tumors are carcinoids. However, among our 25 carcinoids only 5 were appendiceal. Probably the reason for this low incidence is the fact that appendectomy is rarely performed at our hospital for acute appendicitis, most appendices examined pathologically being removed incidentally during abdominal operations for other diseases.

The second commonest site of carcinoids reported in the literature is the ileum. However, in the last few years the incidence of reported cases in the rectum has exceeded that in the ileum, and it is our belief that, with the present keen appreciation of the value of routine proctosigmoidoscopic examination, in the future the rectum may even become the commonest site.

GROSS PATHOLOGY AND CLINICAL CLASSIFICATION

All carcinoid neoplasms, regardless of their site of origin or size, are potentially malignant, and if patients with these lesions live long enough metastases will occur. Some carcinoids reach tremendous size with extensive local infiltration and invasion but no evidence of distant metastases, whereas others may be small but ulcerated and associated with widespread metastases, as in the case of a man aged 71 years reported by Siburg.[12] Carcinoids are like adenocarcinoma in that they spread by infiltration and via the lymph and blood channels, but they are different from them in that they are low-grade and slow-growing, demonstrating apparently benign clinical behavior in the early stage of development. Patients with widespread metastases have been known to remain in apparent good health and live comfortably for many years, especially if the primary carcinoid is removed. The usual cachexia that accompanies adenocarcinomatosis is conspicuously absent in most patients having carcinoids with associated widespread metastases.

We have observed that the clinical behavior of small lesions is unique in that they may be present for a long time without gross evidence of clinically malignant characteristics. This suggests a gross pathologic classification of carcinoid neoplasm that proves extremely helpful in determining the best type of treatment in the individual case. Thus, carcinoids may be classified into clinically benign or clinically malignant.

Clinically benign carcinoids are typically small firm oval well-circumscribed nodules found in the submucosa of the intestinal tract. They project into the intestinal lumen, resembling a sessile polyp. They vary in size from 0.2 to 1.5 cm.; 14 of the 15 rectal carcinoids observed by us were less than 1 cm. in size. These small nodules are covered by a thin intact mucosa that permits detection of the vascular pattern covering the surface of the tumor. They are freely mobile in the submucosa and give the impression of being pseudoencapsulated. The color as seen through the proctoscope is characteristically light yellow, with a waxy appearance, but it may vary from gray to orange.

Clinically malignant carcinoids, in contrast to the clinically benign ones, are grossly larger lesions, usually ulcerated and fixed to their adjacent tissue by infiltration into the submucosa and muscularis. In advanced stages they will manifest all the clinical characteristics of and be indistinguishable from adenocarcinoma of the intestine, in that they may be large polypoid, ulcerative, or circumscribing lesions. Grossly, these neoplasms cannot be diagnosed, but a yellow-colored growth may make one suspicious of the diagnosis. Even a small lesion, if ulcerated or fixed by indurated infiltration, should be clas-

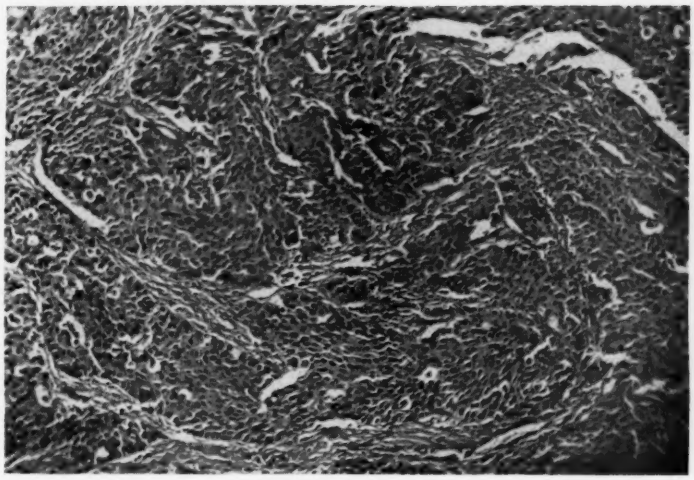

Fig. 2.—Photomicrograph of carcinoid tissue showing cords, ribbons, and solid nests; reduced from mag. ×80.

sified as a clinically malignant carcinoid. Of course, distant metastasis is definite evidence of malignant behavior.

MICROSCOPIC CHARACTERISTICS

In 1939 Ariel and co-workers [13] gave an excellent histologic description of carcinoids. The tumor is composed of compact nests of cells that may appear as solid sheets, thin cords or strands, or pallisading. There is a variable amount of fibromuscular stroma and often a tendency to form pseudoglands or rosettes (Fig. 2). This occurs if the cells are of the columnar or cuboidal type, with basally situated nuclei. There are no true lumens in these rosettes, but the center is frequently filled with homogenous eosinophilic material. The carcinoid cells are generally polygonal with indistinct boundaries and have centrally located nuclei that are spherical with sharp borders. These cells have a moderate amount of cytoplasm, which contains basally situated granules that often stain with silver.

COMMENT

Upper Gastrointestinal Tract.—Carcinoids in the upper gastrointestinal tract, as well as those in the colon, grow silently, and there is a varied long period during which they produce no symptoms. The diagnosis is not made until the advanced stages produce symptoms of acute or chronic recurrent intestinal obstruction by knuckling of the intestine, neoplastic napkin-like stenosis, or a gastrocolic fistula or metastases, especially to the liver. The reported incidence of metastases from ileal carcinoids is from 30% to 53%. This high incidence is probably due to the long symptomless period of the slow-growing lesion, which usually delays the diagnosis until laparotomy, when it may be suspected. However, final diagnosis is dependent on histologic examination. Lesions are multiple in 14% to 25% of cases and are found in older patients than are appendiceal carcinoids.

The ileum is the most frequent site of carcinoid in the upper gastrointestinal tract. In 4 of our 25 cases it was located in the upper gastrointestinal tract. One carcinoid was in the gastrocolic ligament; one, in the liver, diganosed by percutaneous liver biopsy, and two, in the terminal ileum. Three of the four patients had distant metastases.

Appendix.—Carcinoids of the appendix may produce symptoms of acute obstructive appendicitis that result in their removal before they have attained an appreciable size. Also, they are often incidentally observed in appendices removed concurrently during other procedures. The diagnosis is always made by histologic examination. In our cases the tumor was usually a 1.5 cm. yellowish nodule at the tip of the appendix, obliterating the lumen. Approximately 75% of the reported cases are found in women, and four of

our five cases were women. The average age of the reported cases is 25 to 30 years. The small discrete appendiceal carcinoids may be classified as clinically benign, for rarely are they associated with metastases. LeBrun [14] could find only 18 cases of malignant appendiceal carcinoids in the literature, 11 of which had metastases.

Colon.—Carcinoids of the colon are the most highly malignant of carcinoids in the gastrointestinal tract. We were able to collect from the literature 51 cases of carcinoids in this region, of which 43 were malignant, an incidence of 84%. The greater potential for malignancy in the colon is probably due to the larger diameter of the colon, which permits a longer period of growth before the diagnosis is made. Roentgenologically, advanced carcinoid lesions of the colon cannot be distinguished from carcinoma.

We have seen only one case. It is of sufficient interest to warrant brief mention here. The patient was a white man 60 years of age. He was seen in the Ochsner Clinic in August, 1954, complaining of inability to swallow solid foods. A large gastrocolic fistula was found. Subtotal gastrectomy and transverse colectomy were performed, with removal of the tumor, fistula, and omentum en bloc. The mass with the fistulous tract through the central portion measured 7 by 7 by 5 cm. The pathologic diagnosis was "carcinoid tumor of the transverse colon invading the pericolic tissue and producing a gastrocolic fistula." No lymph nodes showed metastatic involvement. This case has been reported in more detail elsewhere.[16]

Rectum.—Reports of rectal carcinoids have been appearing with increasing frequency in recent years. Most of these are clinically benign. Of 164 cases we collected from the literature, only 29 were clinically malignant, an incidence of approximately 17%. This low incidence of clinically malignant lesions is probably the result of the rectal carcinoid being discovered by proctologic examination early, when it is in the clinically benign stage. It is for this reason that we urge that proctosigmoidoscopic examination be a routine part of the complete physical examination. Only 1 of our 15 patients with rectal carcinoids had symptoms, the other 14 being detected during routine proctoscopic examination or when the examination was performed because of symptoms suggestive of hemorrhoids, fissure, or fistula. Fourteen of the fifteen lesions were clinically benign. They ranged in size from 0.2 to 1 cm.

The only rectal carcinoid that produced symptoms was classified as clinically malignant and is of sufficient interest to warrant a more detailed report. The patient, a white man, 31 years of age, was first seen in June, 1952, because of itching in the perianal area and frequent occurrence of bright red blood in the stools for one year. He had been hospitalized elsewhere and was found to have a rectal mass from which a specimen for biopsy was obtained. He was informed that he had cancer of the rectum. On examination by one of us the rectal mass was felt and seen 5 cm. above the anus on the right anterior rectal wall. It was 1.5 by 3.5 cm. in size, fixed, and granular, with a depressed ulcerated surface. The clinical impression was adenocarcinoma, although it was not typical. The specimen obtained at biopsy was reported as "atypical glandular carcinoid." The lesion was malignant and invasive. The patient did not remain for the recommended abdominoperineal resection.

It is usually possible to make a clinical diagnosis of rectal carcinoid if the condition is kept in mind. In the majority of the rectal carcinoid neoplasms in our series a clinical diagnosis was made. Occasionally, we have also made a clinical diagnosis in patients whose tumor proved to be a fibroma, lymph node, or submucosal phlebolith. There are several proctologic observations of clinically benign carcinoid neoplasm which should suggest the diagnosis. First, the lesion is usually a small (0.2 to 1 cm.) hard, fibrotic, freely movable, slightly yellow or gray submucosal nodule producing a sessile polyp (Fig. 3). On biopsy the overlying mucosa is thin and not fixed to the tumor. Owing to its mobility and hardness, the tumor is difficult to

grasp with the biopsy forceps, but once this is accomplished it often is removed from its bed en masse. The defect left by removal gives the impression that an encapsulated tumor has been enucleated.

Our criteria for making a diagnosis of clinically malignant rectal carcinoid are as follows: (1) lesions 2 cm. or over in size (this is an arbitrary measurement, but we believe that tumors of this size are undergoing malignant change and are therefore too large to treat safely by local measures); (2) annular lesions; (3) ulcerated and (4) fixed or indurated lesions; (5) demonstrable metastases in surrounding lymph nodes, and (6) recurrent tumors.

Fig. 3.—Typical appearance of rectal carcinoid as seen through the proctoscope.

Treatment of rectal carcinoids is dependent upon the clinical classification. Our 14 rectal carcinoids that produced no symptoms and were diagnosed as clinically benign were treated by biopsy excision of the neoplasm with wide deep fulguration. In the beginning of our experience with these tumors, if after fulguration the pathologic diagnosis was carcinoid neoplasm the patient was admitted to the hospital and the fulgurated site was excised locally. Residual tumor was not found in any instance. In later cases biopsy excision with wide deep fulguration in the office has been the rule. Only two patients were given an anesthetic for primary biopsy excision with fulguration in the hospital. All patients have been examined by us or their local physician at 6- to 12-month intervals, and all are well, with no evidence of recurrence. The treatment of clinically malignant rectal carcinoids is radical excision, which means abdominoperineal resection. Treatment of carcinoids elsewhere in the gastrointestinal tract, with the exception of appendiceal carcinoids that have no obvious malignant changes, is radical excision, as for carcinoma.

SUMMARY

Twenty-five patients with carcinoid tumors of the gastrointestinal tract have been seen in the Ochsner Clinic between 1943 and 1954. Fifteen of the patients had carcinoids in the rectum; five, in the appendix; one, in the transverse colon, and four, in the upper gastrointestinal tract.

Particular attention has been focused on carcinoids of the rectum. We believe that the rectum is the most common extra-appendiceal site of carcinoid tumors and, further, that all of these tumors are potentially malignant. The recommended treatment of carcinoid is complete local or biopsy excision with adequate destruction by wide deep fulguration for the clinically benign and radical extirpation for the clinically malignant neoplasms.

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Clinical Observations on Hepatic Fibrosis

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The pathogenesis,* biological effects,† and reversibility ‡ of hepatic fibrosis have been extensively studied in experimental animals. Difference in structure and physiology of the liver in humans and in lower vertebrates prevents direct application of these findings to man.[12] Postmortem observations § and in vivo biopsies ‖ correlated with animal experiments provide a background for additional study. This paper records further clinical observations on the histogenesis, significance, and influence of therapy on hepatic fibrosis. The study is based on serial needle biopsies of the liver correlated with clinical and biochemical abnormalities.

MATERIALS AND METHODS

Clinical material included 237 patients with nutritional liver disease, 41 with extrahepatic biliary obstruction, 30 with viral hepatitis, and 75 with congestive heart failure. Liver-function tests used in these patients included determination of serum bilirubin,[26] serum alkaline phosphatase,[27] sulfobromophthalein excretion,[28] serum cholesterol and esters,[29] serum albumin and globulin,[30] cephalin flocculation,[31] thymol turbidity,[32] prothrombin time,[33] and glycogen storage capacity.¶ Needle biopsy of the liver was performed with the Vim Silverman needle, without complications.[36] Biopsy sections were routinely fixed in formalin, and the paraffin section was stained with hematoxylin and eosin, the trichrome stain of Gomori, and/or the connective tissue stain of Mallory. Reticulum stains were applied to selected biopsy specimens.#

Biopsy specimens were classified as exhibiting mild, moderate, or severe fibrosis on the basis of amount and character of fibrosis and dissociation of parenchymal cells from the vascular and biliary systems.[39] In mild fibrosis the connective tissue was young, appeared in thin bands in the centrilobular or periportal area, and occupied less than 10% of the histological section (Fig. 1*A*). Moderate fibrosis was characterized by well-developed connective tissue which contained newly formed blood vessels. The fibrotic process occupied over 10% of the section and was associated with bile duct proliferation and nodular regeneration of liver cells (Fig. 1*B*). In severe fibrosis, connective tissue virtually isolated parenchymal cells and caused complete distortion of the lobular pattern (Fig. 1*C*).

OBSERVATIONS

Histogenesis.—Twenty patients with an initial histological section which exhibited no connective tissue abnormality had repeat biopsies during the evolution of hepatic fibrosis. Fifteen patients with mild fibrosis at the time of original study were subjected to biopsy after progression of the pathological process. Nutritional deficiency, biliary obstruction, passive congestion, and viral hepatitis produced similar degrees of fibrosis (Table 1). The fibrotic process began in the central and/or periportal area.*

Serial biopsies stained for reticulum and/or collagen were used to evaluate mechanisms proposed for the development of hepatic fibrosis: (*a*) proliferation of connective tissue in the site of liver-cell injury,[14] an in-

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* References 1-6.

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‡ References 9-11.

§ References 13-20.

‖ References 21-25.

¶ References 34 and 35.

\# References 37 and 38.

* References 40 and 41.

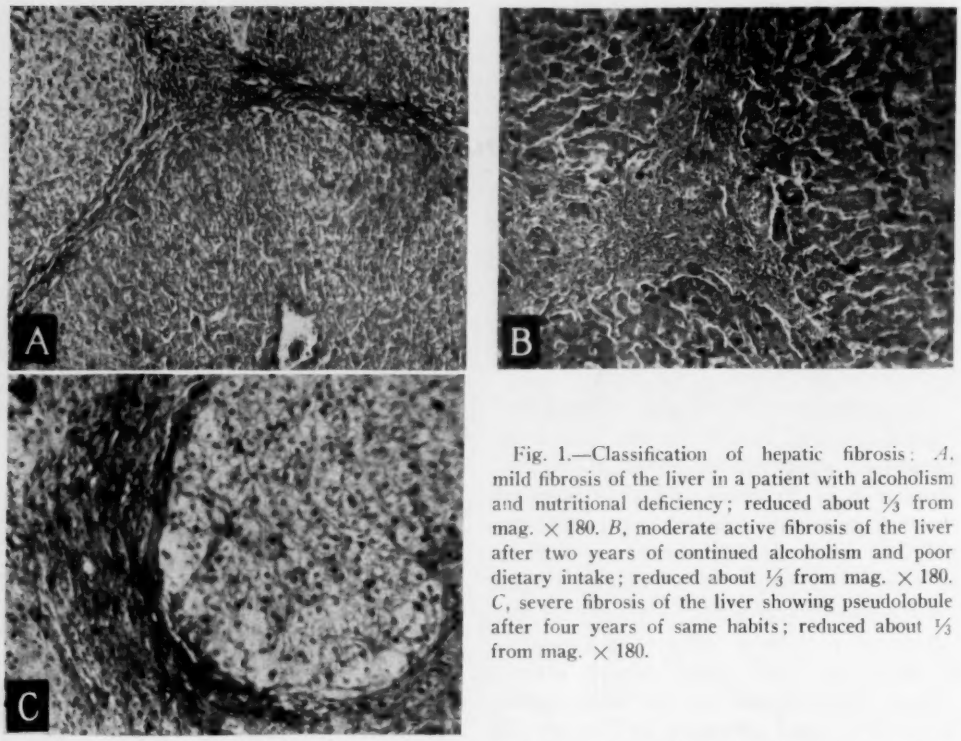


Fig. 1.—Classification of hepatic fibrosis: *A*, mild fibrosis of the liver in a patient with alcoholism and nutritional deficiency; reduced about ⅓ from mag. × 180. *B*, moderate active fibrosis of the liver after two years of continued alcoholism and poor dietary intake; reduced about ⅓ from mag. × 180. *C*, severe fibrosis of the liver showing pseudolobule after four years of same habits; reduced about ⅓ from mag. × 180.

TABLE 1.—*Clinical, Biochemical, and Histological Alterations with Evolution of Mild Hepatic Fibrosis*

	A		B		C		D	
	L. B., Aged 50, Housewife, Fibroblastic Transformation of Fatty Liver		A. S., Aged 80, Retired, Transition of Biliary Hepatitis to Biliary Fibrosis (Ca Head of Pancreas)		P. K., Aged 27, Laborer, Appearance of Fibrosis in Viral Hepatitis		A. K., Aged 49, Unemployed, Development of Centrilobular Fibrosis in Heart Failure (Rheumatic Heart Disease)	
	6/22/48	11/22/52	7/28/53	8/23/53	3/1/52	3/22/52	11/14/52	12/20/53
Clinical data								
Hepatomegaly, cm.	4	5	8	10	6	8	6	8
Splenomegaly, cm.	0	1	0	0	0	1	0	0
Spider angiomata	0	1+	1+	1+	0	2+	0	0
Icterus	0	1+	3+	3+	2+	3+	1+	1+
Fluid retention	0	1+	0	0	0	0	2+	2+
Hepatic fetor	1	1+	0	0	0	0	0	0
Sensorial changes	0	0	0	0	0	1+	0	0
Bleeding esophageal varices	0	0	0	0	0	0	0	0
Biochemical data								
Serum bilirubin, mg./100 cc.	0.3	2.2	26.0	40.0	18.4	28.4	2.6	2.8
Sulfobromophthalein retention, %	6	32	..	..	..	..	16.5	23.5
Alkaline phosphatase, B.U.	2.2	6.5	15.3	19.5	..	..	7.0	..
Serum cholesterol, mg./100 cc.	171	138	232	213	362	582	144	182
Cholesterol esters, mg./100 cc.	82	79	36	10	103	77	101	92
Serum albumin, gm./100 cc.	3.2	2.5	3.1	2.5	2.6	2.6	3.3	3.0
Serum globulin, gm./100 cc.	3.1	5.0	2.4	2.9	3.6	4.2	4.2	4.2
Cephalin flocculation	1+	2+	Neg.	Neg.	2+	4+	Neg.	2+
Thymol turbidity, units	5.0	5.0	0.5	1.0	4.0	20.0	3.0	3.0
Histological findings								
Fibrosis	0	2+	0	1+	0	1+	0	1+
Connective tissue activity	0	2+	0	2+	0	2+	0	1+
Fat	3+	0	0	0	0	0	0	0
Regeneration	2+	3+	2+	2+	2+	2+	1+	1+
Bile stasis	0	1+	3+	4+	0	1+	0	0
Inflammation	2+	2+	2+	3+	2+	3+	1+	0
Necrosis	0	0	0	0	2+	2+	0	0
Blood stasis	0	0	0	0	0	0	2+	2+

Fig. 2.—Fibroblasts in tissue culture from moderate active nutritional cirrhosis. Similar growth was noted in normal liver biopsy specimen (courtesy of Dr. Paul A. Eichorn, Lederle Laboratories, Pearl River, N. Y.); reduced about ⅓ from mag. × 360.

flammatory reaction,[15] or serous exudation,[42] and (*b*) condensation of reticular fibers following destruction of liver cells [1] or collapse of fatty cysts.[3] Our observations suggest that both of these mechanisms are important. Fibrogenesis in the setting of an inflammatory reaction was the more prominent of these phenomena. It was found with and without liver-cell necrosis and was responsible for converting a localized process into a diffuse one. The degree of fibroblastic transformation varied directly with the inflammatory reaction and inversely with liver-cell necrosis. Serous exudation was present with an inflammatory reaction but could not be identified as the sole precursor of hepatic fibrosis.

Fibroblasts, ground substance, and collagen fibers were identified in the connective tissue stroma of hepatic cirrhosis. Fibroblastic activity was assayed by quantitative analysis and morphological characteristics of fibroblasts.† Fibroblasts, which play a central role in connective tissue formation, being directly or indirectly responsible for deposition of ground substance and development of reticular fibers,‡ readily grew in tissue cultures of normal and cirrhotic liver biopsy specimens (Fig. 2).

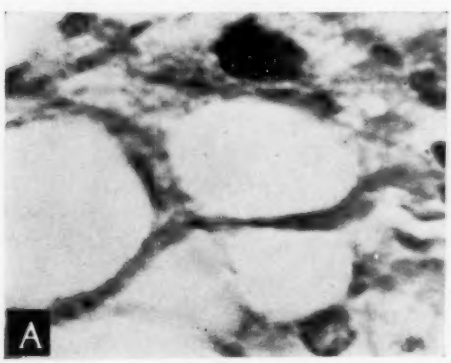
Morphological studies revealed stages in the transition of fatty liver, due to poor dietary habits, to nutritional cirrhosis.[21] Conglobation of intracellular fat led to large fat globules which displaced the liver cell nucleus and formed fatty cysts. Rupture of these cysts, surrounded by reticulum, was associated with an inflammatory reaction and followed by condensation of reticular fibers to form connective tissue septa (Fig. 3). Spindle-shaped fibroblasts and inflammatory cells could be detected in the newly formed connective tissue. Septum formation was demonstrated in the centrilobular as well as periportal areas in early nutritional cirrhosis.

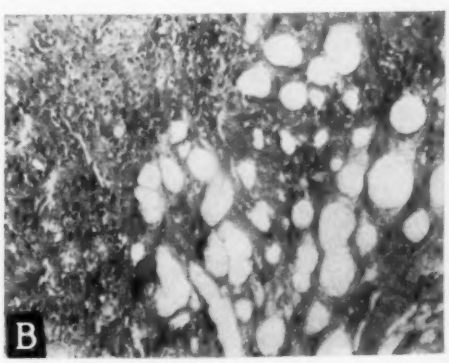
Patients with extrahepatic biliary obstruction showed an inflammatory reaction during the evolution of biliary fibrosis.[22] In the first few weeks of biliary obstruction there was an accumulation of polymorphonuclear cells,

† References 43-46.

‡ References 47-49.

Fig. 3.—Fibroblastic transformation of fatty liver: *A*, large fat globules surrounded by reticulum merging to form fatty cysts; reduced about ⅓ from mag. × 360. *B*, collapse of fatty cysts with surrounding areas of inflammation and fibrosis; reduced about ⅓ from mag. × 180.





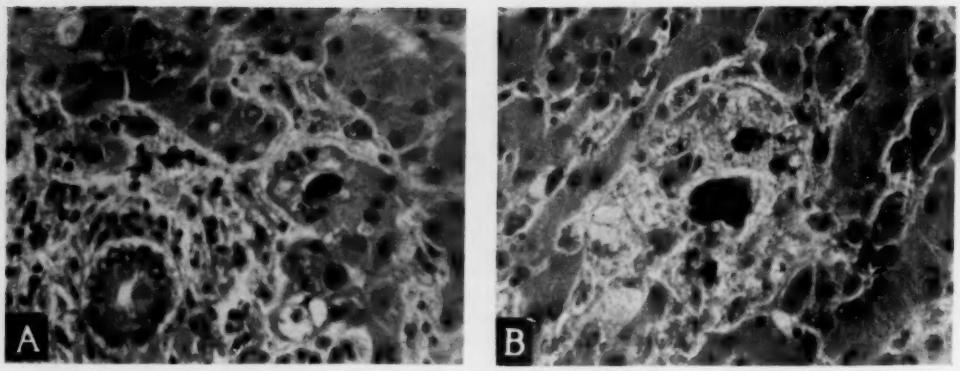


Fig. 4.—Fibrogenesis in extrahepatic biliary obstruction: *A*, portal area, demonstrating bile stasis and mild inflammation during second week of biliary obstruction; reduced about ⅓ from mag. × 360. *B*, fibroblasts and increased collagen in portal area after six weeks of biliary obstruction; reduced about ⅓ from mag. × 360.

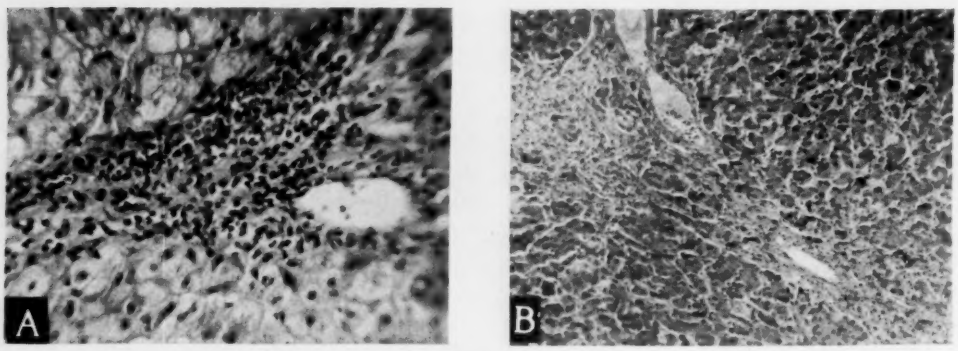
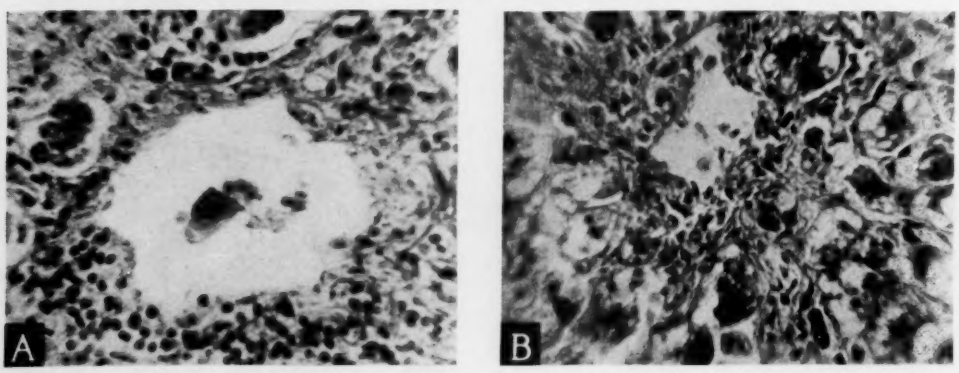


Fig. 5.—Changes in chronic viral hepatitis leading to hepatic fibrosis: *A*, interlobular and intralobular inflammatory reaction in viral hepatitis; reduced about ⅓ from mag. × 180. *B*, fibrotic reaction involving interlobular and periportal areas during healing phase; reduced about ⅓ from mag. × 180.

Fig. 6.—Initial morphological changes in congestive heart failure: *A*, central necrosis with inflammatory reactions in congestive heart failure; reduced about ⅓ from mag. × 180. *B*, centrilobular fibrosis in congestive heart failure; reduced about ⅓ from mag. × 180.



lymphocytes, and monocytes in the portal areas. Cellular infiltration was noted around the portal triad and terminal bile ducts. Subsequent biopsy showed bile-duct proliferation, inflammation, fibroblasts, and an increase of collagen fibers (Fig. 4). Fibrosis involved the entire lobule after a period of several months and divided the parenchyma into pseudolobules.

An inflammatory reaction was also prominent in patients with viral hepatitis who developed hepatic fibrosis. This was characteristic of subacute fulminant hepatitis, where autolytic necrosis was followed by collapse of reticular fibers and large areas of liver parenchyma were replaced by connective tissue, as well as with mild chronic hepatitis, where subsequent biopsy showed ingrowth of fibrous tissue (Fig. 5).[25] Similar reactions have been noted in patients developing hepatic fibrosis as a sequel to infectious mononucleosis,[50] brucellosis,[51] sarcoidosis,[52] and chemical intoxication.[53]

In vivo documentation of events leading to fibrosis of the liver in heart failure was difficult because of inability to obtain long-term follow-up studies of patients with chronic circulatory congestion.[24] Heart failure was characterized by passive congestion and exudation in the space of Disse. Central necrosis developed with severe anoxia and was associated with a centrilobular inflammatory reaction which underwent organization with recovery (Fig. 6). This, coupled with capillary sclerosis and condensation of the reticular stroma, appeared to initiate the fibrotic process. Recurrent episodes of heart failure led to diffuse fibrosis.

Clinical Significance.—The use of serial study techniques facilitated correlation of clinical and morphological findings. Although there was frequently no relationship between morphology and other findings on random studies,§ comparative sequential observations provided good correlation.[39] Signs and symptoms and biochemical changes were related to activity in the connective tissue stroma and to the degree of interruption of normal vas-

§ References 54 and 55.

TABLE 2.—*Correlation of Fibrosis with Biochemical Functions and Clinical Findings* *

Histological Diagnosis	Cases, No.	Excretory Function Abnormalities, Cases, %				Metabolic Function Abnormalities, Cases, %				Clinical Changes, Cases, %			
		BSP Ret.	Elev. Serum Bil.	Elev. Alk. Phos.	Elev. Total Chol.	Abn. Prot. Part.	Pos. Ceph. Floc.	Pos. Thym. Turb.	Abn. Chol. Part.	Jaundice	Ascites	Hepato-megaly	Spleno-megaly
Mild fibrosis, etiology													
Heart failure	9	11	44	33	94	100	44	11	22	11	100	55	11
Biliary obstruction	17	100	100	94	82	88	41	23	64	100	17	100	0
Nutritional deficiency	22	60	50	31	45	40	31	31	45	50	36	86	5
Moderate to severe fibrosis, etiology													
Heart failure	9	100	66	22	11	100	33	11	33	44	100	66	33
Biliary obstruction	12	100	100	91	50	100	66	33	66	100	25	100	75
Nutritional deficiency, moderate	132	70	53	48	37	48	38	23	70	45	48	88	18
Nutritional deficiency, severe	60	90	67	55	40	100	67	30	67	58	56	80	20
Postnecrotic scarring	10	100	80	20	60	100	60	20	30	50	80	60	60

* Biopsies showing necrosis are not included.

cular, biliary, and lymphatic relationships, both of which reflect the functional status of parenchymal cells. Clinical abnormalities were also correlated with necrosis, fat, inflammation, nodular regeneration of liver cells, and bile-duct proliferation.

Patients with mild nonactive hepatic fibrosis exhibited few signs and symptoms; stromal activity and moderate to marked fibrosis with loss of normal lobular architecture was accompanied by clinical evidence of hepatic insufficiency. Biochemical function tests showed a decrease in excretory and metabolic capacity with progression of activity or severity of fibrosis (Table 2). Fibroblastic transformation of fatty liver was accompanied by icterus, splenomegaly, fluid retention, increased retention of sulfobromophthalein (Bromsulfalein), and appearance of positive flocculation tests (Table 1, A). Biliary obstruction leading to hepatic fibrosis was associated with an increase of excretory dysfunction, protein and cholesterol abnormalities, and signs of hepatic decompensation (Table 1, B). Persistent alteration of clinical and biochemical abnormalities characterized development of fibrosis of the liver in patients with viral hepatitis (Table 1, C). Centrilobular and diffuse fibrosis in congestive heart failure were not accompanied by definitive biochemical or clinical features (Table 1, D).

Superimposition of necrosis or fatty changes on a fibrotic liver caused significant deterioration of clinical and biochemical reserve. Prognosis was correlated with the severity of fibrosis when other factors were equal. A review of nutritional liver disease showed that none of the patients with mild fibrosis died of their disease. In contrast, 26% of patients with moderate fibrosis and 50% of those with severe fibrosis died within one year of initial observation.[39] Immediate prognosis in patients with fibrosis depended on other anatomical findings and biochemical reserve. Prognosis was poorer with necrosis, marked disturbance of biochemical liver-function tests, blood clotting abnormalities, and electrolyte depletion. Jaundice, ascites, hematemesis, and mental changes were accompanied by rapid downhill courses. Only 20% of the patients with nutritional cirrhosis and these clinical features were alive at the end of five years.[39]

Influence of Therapy.—Increased connective tissue activity and a transition from mild to moderate to severe hepatic fibrosis was noted when therapy was not available or successful. Although the fibrotic reaction served as a reparative mechanism, necrosis and inflammation often continued or increased with connective tissue proliferation. Therapy in patients with mild fibrosis caused improvement in clinical, biochemical, and histological abnormalities. Regeneration of parenchymal cells improved hepatic architecture when proliferation of connective tissue led to hepatic fibrosis and returned it to normal when condensation of reticular fibers was primarily responsible.

A five-year follow-up study of patients receiving optimum treatment for mild and moderate fibrosis due to nutritional liver disease showed subsidence of inflammation in the connective tissue stroma, disappearance of fibroblasts, decrease in "ground substance," and shrinkage of collagen fibers (Table 3, A) (Fig. 7). This was accompanied by improvement of jaundice, fluid retention, and abnormal liver-function tests.[56] In severe fibrosis the fibrotic process remained unchanged, although fat and hyaline necrosis disappeared. Occasionally, parenchymal changes were first noted in patients with severe hepatic fibrosis during controlled inpatient therapy. This was attributed to difficulty in maintaining normal cell nutrition because of connective tissue barriers, nodular regeneration of liver cells, and formation of arteriovenous shunts.

Surgical relief of biliary obstruction caused the disappearance of clinical, biochemical, and histological abnormalities in patients with connective tissue changes limited to the periportal area (Table 3, B). Portal inflammation, fibroblasts, and increased collagen tissue could not be demonstrated on biopsy sections obtained one to two years after removal of common duct stones.[22] Patients with moderate fibrosis of the liver continued

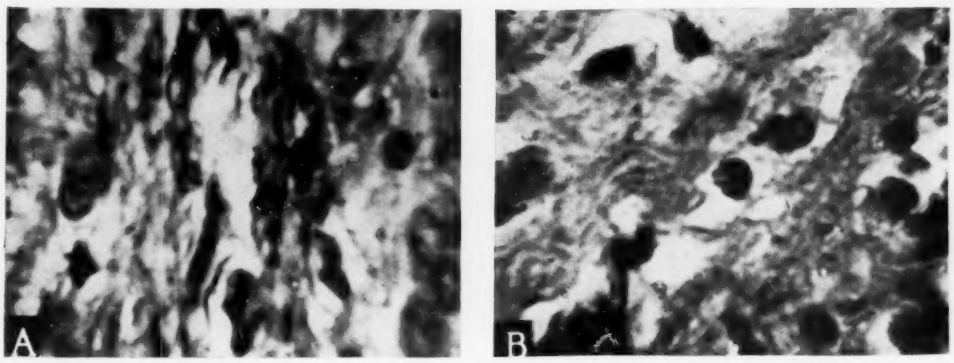


Fig. 7.—Influence of therapy on connective tissue stroma: *A*, fibroblasts and inflammatory cells in moderate nutritional cirrhosis; reduced about ⅓ from mag. × 360. *B*, connective tissue stroma after four years of therapy, showing lymphocytes without fibroblasts; reduced about ⅓ from mag. × 360.

TABLE 3.—*Influence of Therapy on Clinical, Biochemical, and Histological Alterations in Patients with Hepatic Fibrosis*

	A W. S., Aged 57, Laborer, Nutritional Deficiency (Diet)		B L. W., Aged 57, Housewife, Biliary Obstruction (Removal of Common-Duct Stone)		C V. C., Aged 30, Housewife, Viral Hepatitis (Rest, Diet)		D W. M., Aged 38, Laborer, Heart Failure (Rest, Cardiotherapy)	
	1/3/50	1/29/54	6/28/52	12/12/53	8/10/54	1/9/55	5/20/52	11/12/53
Clinical data								
Hepatomegaly, cm.	6	4	6	0	1	2	4	2
Splenomegaly, cm.	0	0	1	0	0	0	0	0
Spider angiomata	1+	0	0	0	1+	0	0	0
Icterus	2+	0	1+	0	3+	0	1+	0
Fluid retention	2+	0	0	0	0	0	2+	0
Hepatic fetor	0	0	0	0	0	0	0	0
Sensorial changes	1+	0	0	0	0	0	0	0
Bleeding esophageal varices	0	0	0	0	0	0	0	0
Biochemical data								
Serum bilirubin, mg./100 cc.	11.5	0	1.0	0.3	24.0	1.0	2.8	0
Sulfobromophthalein retention, %	..	0	19.5	0	71	0	23.5	0
Alkaline phosphatase, B.U.	4.2	5.0	28.0	3.4	8.3	1.9	..	..
Serum cholesterol, mg./100 cc.	188	291	291	283	268	325	182	190
Cholesterol esters, mg./100 cc.	109	113	181	158	84	176	92	100
Serum albumin, gm./100 cc.	2.4	3.2	2.9	3.5	2.7	3.1	3.0	3.5
Serum globulin, gm./100 cc.	3.4	2.3	3.2	2.1	4.0	3.9	4.0	4.0
Cephalin flocculation	2+	Neg.	3+	Neg.	4+	3+	2+	Neg.
Thymol turbidity, units	2.0	0.5	1.0	2.0	9.5	5.0	3.0	Neg.
Histological findings								
Fibrosis	2+	1+	1+	0	1+	0	1+	1+
Connective tissue activity	2+	0	2+	0	2+	0	2+	0
Fat	2+	0	2+	1+	0	0	0	0
Regeneration	3+	1+	0	0	2+	2+	2+	1+
Bile stasis	1+	0	0	0	1+	0	0	0
Inflammation	2+	1+	2+	0	3+	1+	1+	0
Necrosis	1+	0	0	0	3+	0	0	0
Blood stasis	0	0	0	0	0	0	1+	0

to have connective tissue alterations, although clinical and biochemical abnormalities improved after surgical intervention. There was a progressive downhill course with severe fibrosis despite relief of biliary obstruction. Jaundice, pruritis, xanthomatosis, and biochemical liver functional changes persisted.

Patients with viral hepatitis associated with fibrosis showed spontaneous subsidence of activity in the connective tissue in some instances (Table 3, C) but oftentimes progression, despite therapy. Mild fibrotic reactions due to condensation of reticular fibers were no longer evident after several months of

therapy. Cardiac therapy led to stabilization of centrilobular inflammation and fibrosis in patients surviving episodes of acute heart failure (Table 3, D). No alterations were demonstrable with well-defined centrilobular fibrosis.

It was sometimes possible to anticipate therapeutic response on the basis of activity and severity of hepatic fibrosis. The best results were obtained in patients with mild or moderate active fibrosis. Connective tissue activity and vascularity was used as an additional criterion in the choice of therapy for esophageal varices. Activity in the connective tissue stroma was considered an indication for prolonged medical management. Fluid retention was controlled with a diuretic regimen in patients with mild and moderate fibrosis. Ascites was often refractory to routine therapy with severe fibrosis, although repair of hemoglobin and protein deficits caused temporary mobilization of fluid.

A variety of substances including vitamin B_{12}, broad-spectrum antibiotics, and adrenal steroids, which influence connective tissue stroma in experimental animals, were used as adjuncts to general therapy in patients with mild and moderate fibrosis. Therapeutic response was determined by repeat clinical, biochemical and histological studies at monthly intervals. Results, to date, suggest that antibiotics and adrenal steroids in conjunction with rest, diet, and supportive measures may help suppress inflammatory reactions and fibroplasia in selected patients.‖

COMMENT

This study emphasizes the importance of quantity and activity of connective tissue in hepatic fibrosis. Prognosis and response to therapy in hepatic fibrosis depends upon its mechanism (connective tissue proliferation, condensation of reticulum), degree (mild, moderate, severe), and activity (active, inactive). Connective tissue alterations serve as a suitable gauge for therapeutic orientation; however, constant cognizance must be had of the effects of nodular regeneration of liver cells and other morphological changes in cirrhosis. Acceptance of the value and safety of needle biopsy of the liver, while acknowledging its limitations, is essential for this concept to be of practical importance. Serial evaluation of patients with established liver disease has constituted the chief indication for more than 2000 needle biopsies performed in the Jersey City Medical Center during the past seven years.

A classification based on the type and severity of hepatic fibrosis is important in prognosis and treatment. Physiological and biochemical studies in patients with cirrhosis of the liver are of much greater value when both histological and clinical status is clarified. Difference of opinion relative to the value of available therapeutic programs is due to a lack of histological studies. Reliance on clinical selection permits inclusion of patients with varying degrees of fibrosis in addition to those with fatty liver and other completely reversible anatomical lesions.

Postmortem analysis of the cirrhotic liver shows an actual increase in collagen connective tissue.[57] The important role of connective tissue proliferation in hepatic fibrosis is also revealed by reconstruction of serial sections and statisticogeometric analysis of necropsy material.[18] Condensation of reticulum is sometimes important in early phases of fibrogenesis; active growth of collagen fibers occurs secondarily.

The value of early recognition and treatment of hepatic fibrosis is emphasized by the finding that neither connective tissue proliferation nor condensation of reticuluar fibers due to liver injury is spontaneously progressive. Both may be controlled by therapy. Numerous studies show an improved outlook in cirrhosis of the liver when clinical and biochemical abnormalities are treated.¶ Additional study is required to determine the role of antibiotics, adrenal steroids, and other medicinal agents in long-term management of patients with active fibrotic reactions.

‖ Leevy, C. M., and Zinke, M.: Unpublished data.

¶ References 58-62.

Future attention to the status of the connective tissue stroma as well as parenchymal cells in patients with hepatic fibrosis will provide a new objective in treatment and further define limitations of current therapeutic approaches.

SUMMARY AND CONCLUSIONS

A study of serial needle biopsy of the liver suggests that hepatic fibrosis in man is principally due to proliferation of connective tissue in the site of liver-cell injury, while condensation of reticular fibers is contributory. Hepatic cirrhosis may result from nutritional deficiency, biliary obstruction, toxic and infective agents, passive congestion, or a combination of these factors. These pathogenetic mechanisms may ultimately produce similar clinical, biochemical, and histological changes.

Degenerative and inflammatory changes involving parenchymal cells of the liver are reflected in its connective tissue stroma. Alteration of stromal activity is accompanied by concomitant clinical and biochemical changes.

Diagnostic and therapeutic perspective is improved by determining the severity and activity of hepatic fibrosis. Periodic histological study correlated with clinical and biochemical findings is desirable to evaluate response to therapy.

Fibrosis of the liver is not spontaneously progressive and may be influenced by treatment. Current therapy is effective in control of connective tissue proliferation in patients with mild to moderate active fibrosis. Mild fibrotic reactions due to condensation of reticular fibers are not evident after regrowth of liver cells. Severe fibrosis is usually refractory to treatment, although alterations in parenchymal cells and biochemical and clinical abnormalities improve with appropriate measures.

The experimental background for this paper is based on observations made by Dr. Leevy in the laboratories of Dr. Charles Best and Dr. Stanley Hartroft, of the Banting-Best Department of Medical Research, University of Toronto, during the tenure of an A. Blaine Brower Traveling Scholarship of the American College of Physicians, 1954.

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Drug Therapy (Rauwolfia) of Hypertension

I. Pharmacodynamics of Rauwolfia

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Many recent studies have established the therapeutic effectiveness of Rauwolfia alkaloids, both in internal medicine and in neuropsychiatry. As a consequence, there is great interest in the chemistry, and particularly in the pharmacodynamics, of these alkaloids. Although a chemical study of preparations made from the roots of Rauwolfia serpentina had been attempted toward the end of the 19th century, it was not until 1931 [1] that the alkaloids were subdivided into the two principal groups containing the ajmaline and serpentine alkaloids, respectively. Later other extracts were made from Rauwolfia serpentina. The alseroxylon fraction was prepared in 1952.[2] In spite of the efforts of many investigators, it was not until recently that pharmacologically and clinically active alkaloids were prepared in pure forms. The first such alkaloid to be isolated was reserpine.[3] Some investigators have attributed the hypotensive action of the whole root to this single alkaloid * when used for the treatment of hypertension. However, our observations indicate that additional alkaloids, at least one of which (rescinnamine) has been isolated in pure form,[6] have very definite hypotensive activity (Fig. 1). Rescinnamine has pharmacologic properties which are qualitatively similar to those of reserpine, but it produces less sedation and less bradycardia in proportion to its hypotensive dose than does reserpine.[7] Both the reserpine and rescinnamine content of crude Rauwolfia root vary several hundred per cent from lot to lot. In general, both the crude root and the alseroxylon fraction of Rauwolfia serpentina

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* References 4 and 5.

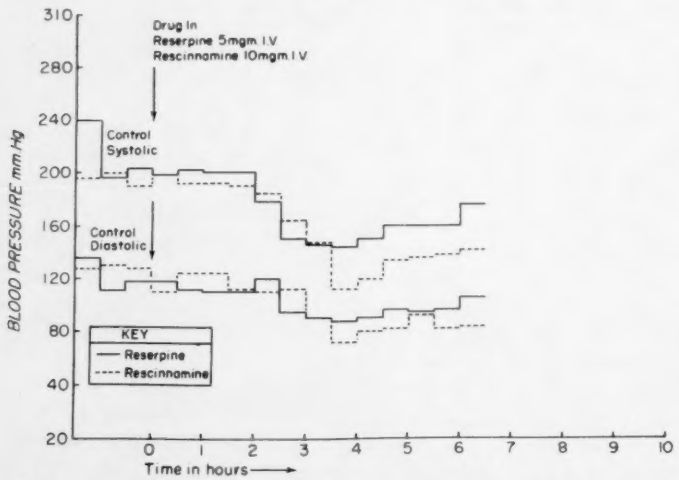

Fig. 1.—Blood pressure response to 5 mg. of reserpine as compared with 10 mg. of rescinnamine given parenterally on different days. (Reproduced with permission from Moyer and others,[17] *American Journal of the Medical Sciences*, Philadelphia, Lea & Febiger.)

contain about 25% as much rescinnamine as reserpine. Rescinnamine is chemically more frangible than reserpine, and some of the available extracts have been found to be relatively low in rescinnamine, suggesting that degradation has taken place in the process of extraction.

GENERAL OBSERVATIONS ON PHARMACODYNAMICS

The Rauwolfia extracts which are commercially available for the treatment of hypertension have, in general, similar pharmacodynamic properties. They reduce the blood pressure by central suppression of vasoconstrictor impulses. This is supported by both clinical and laboratory evidence.† The best clinical evidence of a central type of action is the failure to block the pressor effect of arterenol and the absence of significant orthostatic hypotension, which is a prominent action of both ganglionic and adrenergic blocking agents. Although hypertensive patients may exhibit a significant drop in blood pressure following parenteral administration of reserpine or rescinnamine, which is greatest when the patient stands (Fig. 2), this orthostatic effect is rarely observed following oral administration of either single alkaloids or extracts containing several alkaloids.

Relaxation of the nictating membrane following the administration of reserpine to a dog is as marked as that observed following superior cervical sympathetic ganglionectomy,[10] indicating that the sympathetic nervous system is depressed. Animal studies have shown that this depression of the sympathetic nervous system is not due to peripheral blockade of the sympathetic nervous system, since no interference in splanchnic nerve stimulation is observed[10] and there is no evidence of blockade to the vasopressor response to arterenol and epinephrine. Experimental evidence suggests that ganglionic blockade does not occur, since the synaptic transmission in the superior cervical ganglion of cats is not inhibited by reserpine. Further support to central depression (probably hypothalamic) of the sympathetic nervous system rather than peripheral blockade is given by the observations that reserpine and alseroxylon inhibit pressor reflexes originating in the carotid sinus.‡ The pressor response to hypoxia is also suppressed by both fractions. Inhibition of pressor response to central vagal stimulation has been demonstrated.[5] This blockade of responses to impulses flowing over the peripheral afferent fibers of the

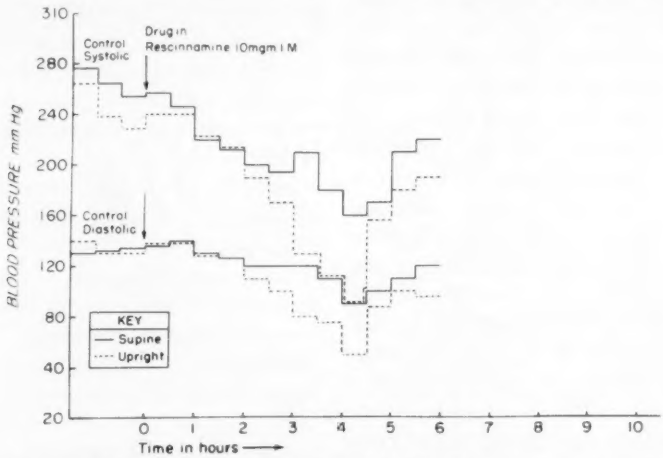

Fig. 2.—A comparison of the supine and upright blood pressure response to parenteral rescinnamine. (Reproduced with permission from Herschberger and others, *American Journal of the Medical Sciences*, Philadelphia, Lea & Febiger.)

† References 8-10.

‡ References 9 and 11.

vagus nerve may be of clinical importance, particularly in patients with so-called labile neurogenic hypertension. Faradic stimulation of the peripheral end of the vagus continues to produce bradycardia and hypotension, indicating an absence of any effect on the vagal system peripherally. The blood pressure effects are not altered by cholinergic blockade, indicating that parasympathetic activity is not responsible for the reduction in blood pressure. These observations lead to the conclusion that the Rauwolfia extracts which are available for clinical use reduce the blood pressure by suppressing the sympathetic nervous system in the brain, which results in a reduction in outflow of vasoconstrictor impulses from the vasomotor centers to the arterioles.

Even more frequently observed than the hypotensive response to Rauwolfia extracts is a slowing of the pulse rate, which may be seen in patients in whom the blood pressure is not reduced. The exact mechanism of this effect has not been clarified. It does not appear to be entirely of vagal origin, since it is only partially blocked by the intravenous administration of atropine. We have studied 15 patients who exhibited bradycardia due to the administration of reserpine or alseroxylon. When these patients were given 1 mg. of atropine sulfate intravenously, the pulse rate increased toward the control value but never exceeded it. Usually it remained about half way between the control level and the rate observed just prior to the administration of the atropine. It is probable that the response to Rauwolfia alkaloids is a result of suppression of the central components of the sympathetic nervous system which innervate the heart. This would explain why Rauwolfia prevents the tachycardia produced by hydralazine (Apresoline), which causes stimulation of the cardiac sympathetics. This effect of Rauwolfia on the pulse rate is an important practical consideration when a therapeutic program is used which combines Rauwolfia extracts with hydralazine, since the pulse-accelerating effect of the latter drug is so well controlled if Rauwolfia is given first. We have also observed that the orthostatic effect produced in the responsive patients on this combination is only slight, and for this reason it may be reasonable to assume that this is the safest approach to the management of elderly patients with hypertension and of hypertensive patients with renal disease.[12] Further, the reflex tachycardia that is frequently seen in the upright position in patients who are receiving adrenergic or ganglionic blocking agents is also blocked for the most part when one of the Rauwolfia extracts is given concurrently. Reserpine does not affect the heart-lung preparation, suggesting the absence of a direct cardiac effect.[10]

The blood pressure response in the dog was used by Cromheim and his associates [2] for standardizing the drug. In this standardization the blood pressure is measured before and after five days of oral administration of the drug to dogs. It was found that a dose of 50γ to 100γ per kilogram of alseroxylon reduced the blood pressure and the pulse rate consistently. In contrast, a dose of 10γ to 25γ of reserpine produced a similar response. According to these observations, the dose-response ratio is about 4 : 1 when alseroxylon is compared with reserpine. This parallels closely clinical observations when the two drugs are used therapeutically for reducing blood pressure. It is interesting to note that the dose-response curve to alseroxylon is identical with that of reserpine except for the dosages employed.[2]

It has been suggested that the hypotensive response of Rouwolfia is due to its sedative properties.[13] However, reserpine or alseroxylon [9] when administered to anesthetized animals [14] effectively lowers the blood pressure. The mild sedative effect of the reserpine could scarcely be responsible for the reduction in blood pressure under these circumstances. Furthermore, in patients with severe hypertension, Rauwolfia may produce a significant reduction in blood pressure under circumstances where sedation alone, even approaching the point of anesthesia, does not lower the blood pressure significantly. Several such examples are illustrated

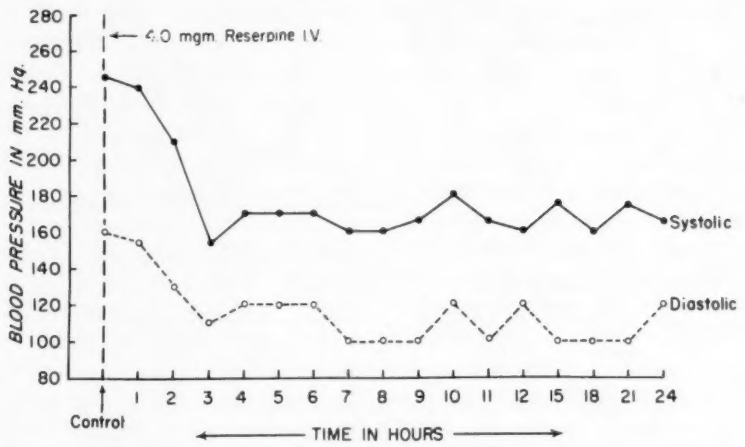

Fig. 3.—Following the administration of 4 mg. of reserpine (parenterally) to a patient with malignant hypertension there is a prompt and maintained reduction in blood pressure. With continued drug administration the blood pressure returned to normotensive levels and remained there. Papilledema and retinal hemorrhages cleared rapidly.

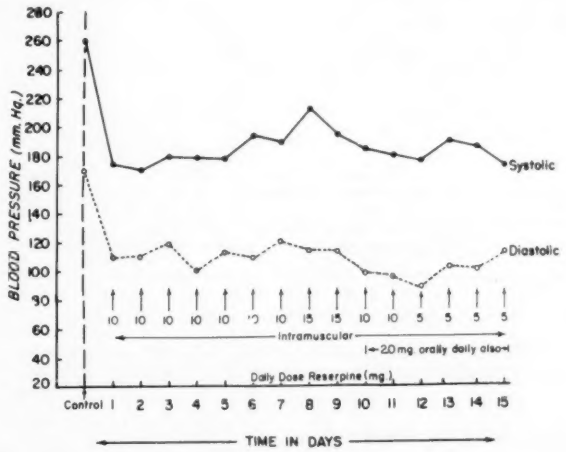

Fig. 4.—Following the parenteral administration of reserpine there was a significant and maintained reduction in blood pressure in a patient with severe cardiovascular disease. A similar response could not be induced with amytal sodium.

in Figures 3 to 7. It seems apparent that parenteral reserpine will lower the blood pressure in patients with hypertension regardless of the cause of the elevation. For example, it was equally effective in patients with malignant hypertensive vascular disease and toxemia of pregnancy (Fig. 5), as well as in patients with hypertension of apparent renal origin such as acute nephritis (Fig. 6) and renal artery occlusion (Goldblatt kidney) (Fig. 7).

It has also been suggested that the drug depresses the basal metabolic rate.[14] In order to evaluate this aspect of the pharmacology, eight patients were studied during the control period by determination of basal metabolic rates and by radioactive-iodine-uptake studies. These studies were repeated after the patients had received 16 mg. (8 tablets) of the alseroxylon extract for from six weeks to three months. There was no significant difference between the control and the post-

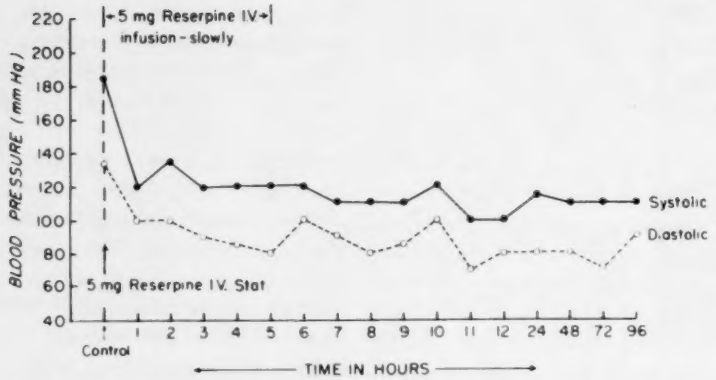

Fig. 5.—Following the administration of reserpine to a patient with toxemia of pregnancy the blood pressure was reduced from hypertensive to normotensive levels. This response was similar to that of a patient with essential hypertension.

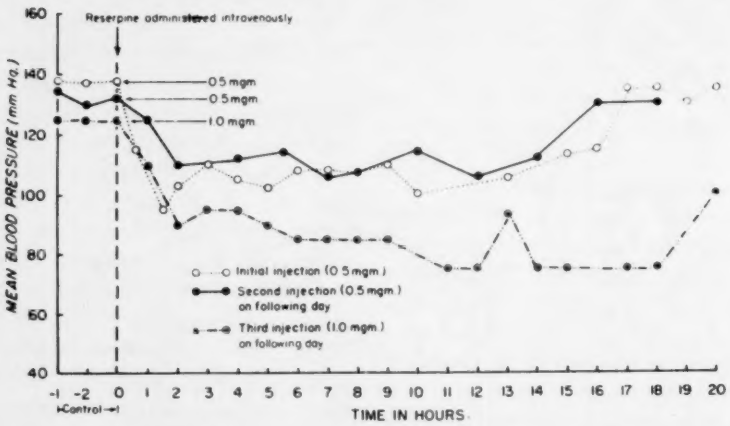

Fig. 6.—Repeated administration of reserpine to a child with acute glomerular nephritis. The blood pressure was reduced similarily to patients with essential hypertension.

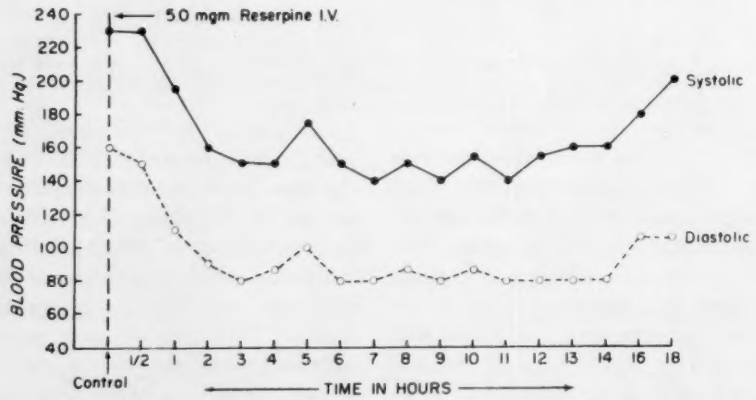

Fig. 7.—Patient with hypertension associated with renal ischemia following unilateral renal artery occlusion. The blood pressure can be reduced with parenterally administered reserpine just as in the case of essential hypertension.

drug observations. The results are summarized in the Table. These observations on basal metabolic rate are at variance with other, similar observations before and after the administration of reserpine.[15]

Although body temperature is lowered moderately in some laboratory animals,[10] no actual antipyretic effect (fever produced with B. coli in rabbits) has been shown in dosage up to 1 mg./kg. given parenterally. However, the heat-regulating center in these animals seems to be influenced by the drug. When they are placed in a high environmental temperature after the administration of reserpine, they show a rise rather than a fall in temperature.

Effect of Rauwolfia on Basal Metabolic Rate and Radioactive-Iodine (I^{131}) Uptake

	BMR		I^{131} †	
Patient	C *	D *	C	D
1	−10	− 2	17	23
2	−10	−23	18	26
3	+ 6	−10	18	16
4	+ 2	− 2	17	20
5	−17	−20	24	20
6	−12	+ 3	17	16
7	+ 2	−18	23	16
8	+10	+11	26	19

* C, control; D, after at least six weeks of Rauwolfia administration.
† Maximum uptake in per cent of I^{131} administered.

SEDATION

When administered either intravenously or orally, reserpine has a marked sedative effect on dogs and other laboratory animals. After small doses the animals are listless and sleepy, but they sleep quietly after larger doses. However, it is typical that even very large doses do not actually anesthetize the animals; they can be awakened readily by external stimuli, falling asleep again when left undisturbed. Even after intravenous injection of the drug, the onset of effect appears only after a latent period of 15 to 45 minutes; this is longer after smaller doses than after larger ones. Following oral administration this latent period is prolonged only slightly. A characteristic observation is the animal's loss of interest in his environment. A cumulative effect is observed after daily administration of the drug, which reaches a steady state after one to two weeks. Tolerance has not been observed after chronic administration to dogs.[10] Even after a single dose the sedative effect is long-lasting, and it may persist for two days in rabbits which have been given relatively small doses. After doses of reserpine of 1 to 5 mg/kg. given intravenously or 20 mg/kg. given orally, this effect may last for six to seven days. A similar duration of response is frequently seen in man.

In patients who are given large doses of either single alkaloids or preparations containing multiple alkaloids, somnolence is not as prominently associated with the reduction in nervous tension as is the case with barbiturates. However, if the dose of Rauwolfia serpentina is adequate, somnolence is observed frequently. This response is particularly apt to occur with patients who are receiving reserpine and occurs over an extremely wide dosage range (1 to 8 mg. per day). It is observed one to two hours after parenteral administration. After oral administration it is frequently not apparent for two to four days, but occasionally it may be observed within several hours. We have seen some patients who could use the drug at night as a soporific agent. When these patients took the drug in the morning, they were very sleepy all day. After chronic oral administration, the sedative effect is entirely lost after two to three months in most patients. A few patients do not lose the sedative response, and it may even increase in the exceptional case. The sedative and soporific response is occasionally followed by exactly the opposite reaction, such as anxiety, restlessness, and insomnia. When somnolence is seen after oral administration, and the drug is discontinued, the somnolence is relieved in about the same period of time as it took to develop, usually within 48 to 72 hours.

RESPIRATORY EFFECTS

Parenteral administration of reserpine to hypertensive patients decreases respiration only slightly. This is most apparent in ap-

prehensive patients and in anxious patients with rapid respiratory rates. Under these circumstances, while the rate is usually decreased, the depth of respiration is increased. There is no significant change in arterial oxygen saturation following the administration of reserpine, indicating that effective pulmonary ventilation is not affected adversely. The drug has actually proved effective for increasing pulmonary ventilation in respirator cases with poliomyelitis who are ill at ease and tense from recent respiratory paralysis. When reserpine is given in lethal doses to laboratory animals, it produces respiratory failure.

GASTROINTESTINAL RESPONSE TO RAUWOLFIA

Reserpine produces an increase in the secretory as well as the motor activity of the intestinal tract. In the dog there is an increase both in volume and in hydrochloric acid content of the gastric secretion.[10] This response is prevented by cholinergic blocking agents, indicating that it probably results from increased parasympathetic activity. In dogs both alseroxylon and reserpine increase intestinal activity to the point of severe diarrhea when sufficiently large doses are administered. When used clinically, increased frequency of bowel movement is seen commonly with all Rauwolfia extracts[7] but diarrhea is relatively infrequent, being seen in only about 5% of the patients receiving the drugs.

CARDIOVASCULAR HEMODYNAMICS

Laboratory observations have been made on cardiovascular hemodynamic responses to reserpine administered intravenously to anesthetized dogs. Cardiac output was determined by the pulse-contour method of Hamilton and Remington.[16] Following control observations, reserpine was given intravenously (3 or 4 mg.) over a period of three to five minutes, and the cardiac output was determined immediately following drug adminis-

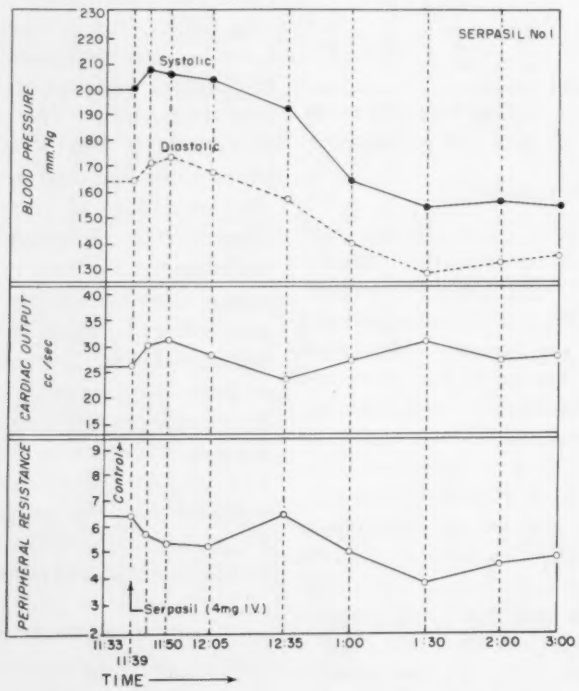

Fig. 8.—Effect of reserpine on the blood pressure in an anesthetized dog. The blood pressure is reduced primarily as a result of a reduction in peripheral resistance (vasodilatation).

tration and every 15 minutes thereafter for the next 4 hours.

The initial cardiovascular response following the intravenous administration of reserpine to dogs varied significantly. A consistent effect on cardiac output was not seen. Occasionaly, a slight decrease or increase was noted, but usually the values did not vary appreciably from the control. After one or two hours there was a slow and gradual decrease of the mean blood pressure to 20 or 30 mm. Hg. below the control level. The blood pressure remained at these reduced levels for two to five hours and then returned slowly to control levels. Although cardiac output was frequently somewhat reduced concurrently with the fall in pressure, this was neither consistent nor necessary for the effect on blood pressure, which was due primarily to a decrease in peripheral vascular resistance.

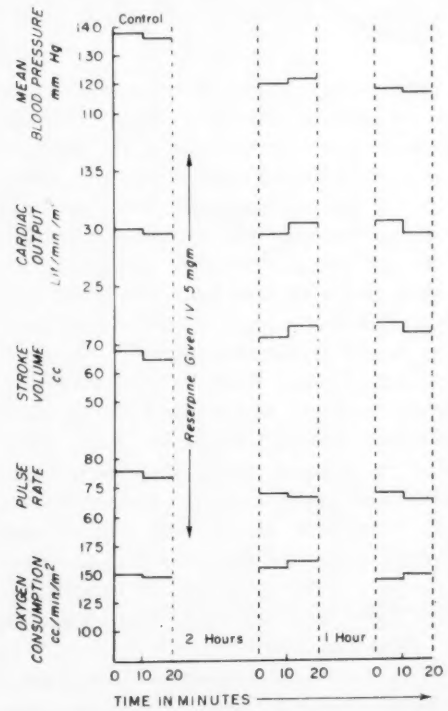

Fig. 9.—Cardiovascular response to parenteral reserpine in a patient with moderately severe hypertension. Two hours after the administration of reserpine there is a significant and maintained reduction in blood pressure. This is associated with a reduction in pulse rate. The stroke volume increases slightly, and, consequently, the cardiac output is not altered despite the reduction in pulse rate.

Similar observations have been made in patients with hypertension (Fig. 9) who did not have heart failure or other serious complications of hypertensive vascular disease. As the blood pressure decreased in these patients, peripheral resistance was decreased without affecting cardiac output. The bradycrotic response was not associated with alterations in cardiac output but rather with an increase in stroke volume.

OBSERVATIONS ON RENAL HEMODYNAMICS

Observations on renal hemodynamics were made on anesthetized dogs according to the methods described previously.[17] Creatinine was used to measure glomerular filtration rate and *p*-aminohippurate was used to measure renal plasma flow. The excretion rates of sodium and potassium and the concentration of these electrolytes in the plasma were determined concurrently. After suitable control observations, 2 to 4 mg. of reserpine was administered intravenously. Blood pressure was determined by direct arterial manometry. Observations on renal hemodynamics were made intermittently for the next four hours.

One to two hours after administration of the drug to dogs the blood pressure was reduced in all of the animals in which the renal hemodynamic response was studied. The average blood pressure during the control period was 152 mm. Hg, and one to one and one-half hours after reserpine administration it had decreased to 117 mm. Hg for the group. After four hours, however, the average mean blood pressure had increased again to 141 mm. Hg. There was no significant alteration of glomerular filtration rate for the group, either initially or after four hours. At the point of maximum blood pressure reduction the average renal blood flow was not altered. After four hours there was a slight depression of renal blood flow for the group, which was probably due to the prolonged anesthesia rather than to the reserpine, since the hypotensive response was relatively insignificant at this time. There

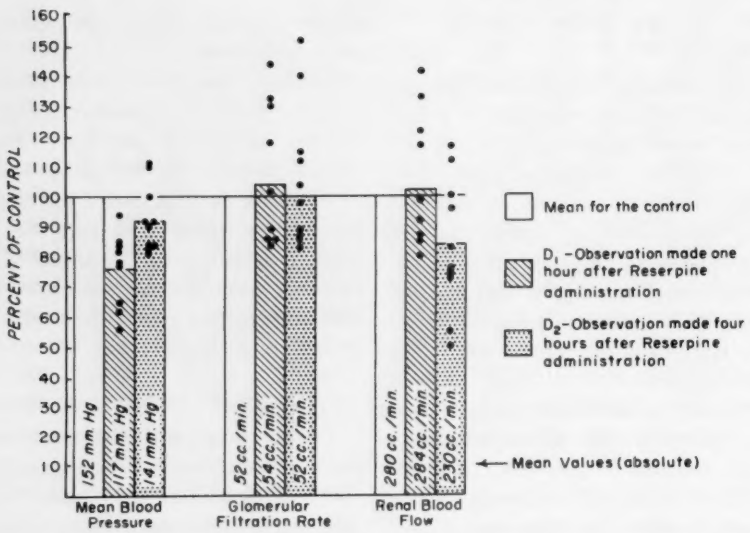

Fig. 10.—Acute renal hemodynamic response to reserpine in the dog. Each observation (black dot) is expressed in terms of the animal's own control. In addition, the mean observations for the group are shown by the bar graph. There are no consistent effects on glomerular filtration rate or renal blood flow. (Reproduced with permission from Moyer, [14] *Annals of the New York Academy of Sciences,* New York, The Academy.)

was no significant effect on renal vascular resistance except at the point of maximal blood pressure reduction, at which time it was reduced in comparison with the control values. The administration of reserpine was not associated with alterations in water or sodium and potassium excretion or in the concentration of these electrolytes in the urine. The renal vasoconstrictor effect of arterenol was not altered by the previous administration of reserpine, indicating that reserpine did not produce adrenergic blockade of the renal vasculature.

Observations on renal hemodynamics were also made on hypertensive patients following the intravenous administration of 1 to 3 mg. of reserpine. Inulin was used to determine glomerular filtration rate, and *p*-aminohippurate was used to estimate renal plasma flow in these hypertensive patients. The excretion rates of sodium and potassium and the concentrations of these electrolytes in the plasma were determined by employing the same techniques used in the animal experiments. Postdrug observations were made intermittently over a period of six hours.

After administration of reserpine, five of the six patients showed a slight reduction in glomerular filtration rate at the point of maximum reduction in blood pressure, which occurred two to three hours after administration of the drug. The sixth patient actually showed a sharp increase in glomerular filtration rate. One hour later, there was very little additional change in either blood pressure or glomerular filtration rate. The average renal blood flow for the group of patients was not affected by blood pressure reduction, although there was some variability in response among the different patients. The excretion of water and electrolytes was reduced in all but one patient, who showed a marked increase. This response may be a direct effect of the drug but is more likely secondary to the slight reduction in glomerular filtration which occurs in these patients and is probably a temporary response prior to hemodynamic readjustment. However, we have observed peripheral edema due to sodium and water retention develop in psychiatric patients who have been given reserpine parenterally in doses of 20 mg. or more per day. There was no evidence

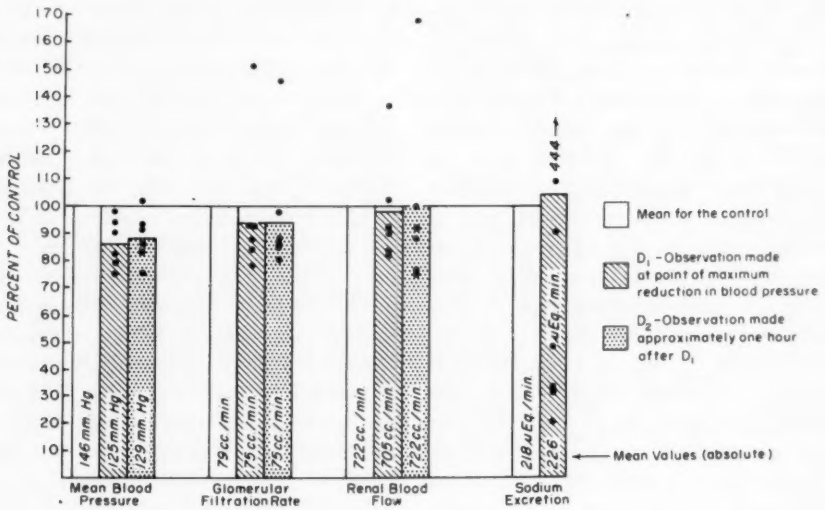

Fig. 11.—Acute renal hemodynamic response to parenteral reserpine (3 mg.) in patients with hypertension. Each observation (black dot) is expressed in terms of the patient's own control observation. As the blood pressure decreased glomerular filtration rate was reduced in all but one patient. This was usually associated with a decrease in sodium excretion.

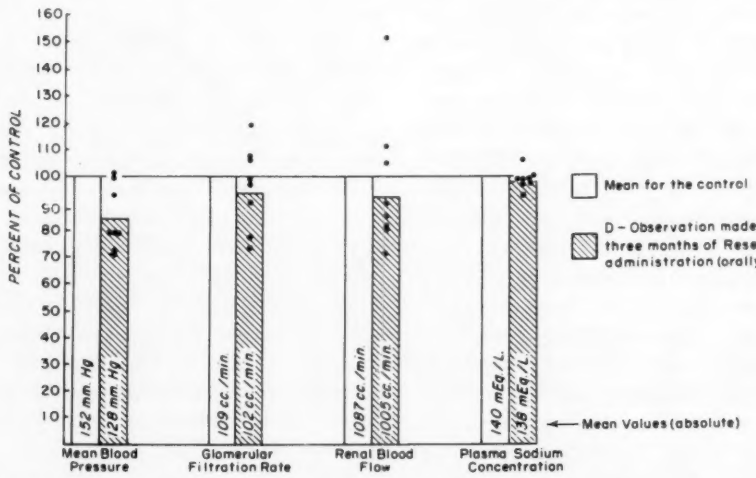

Fig. 12.—Renal hemodynamic response to reserpine administered orally for three months to patients with hypertension. There was no consistent effect on renal blood flow or on glomerular filtration rate. (Reproduced with permission from Moyer,[14] *Annals of the New York Academy of Sciences,* New York, The Academy.)

of a diuretic effect associated with the administration of reserpine in the current study.

Observations were also made on hypertensive patients to whom reserpine was administered orally for three months. After suitable control observations, these patients received 3 to 6 mg. of reserpine daily for the next three months. After this period, renal-function studies were repeated, employing the same techniques that were used for the control studies. Glomerular filtration rate, renal blood flow, and the plasma concentration of sodium and potassium were determined.

Six of the eight patients treated with reserpine for three months or more obtained a significant reduction in blood pressure (fall in mean pressure of more than 20 mm. Hg). Three of the eight patients showed a small increase in glomerular filtration rate; in three it decreased slightly, and in two there was no change. These variations over a three-month period are no more than one could expect in a similar group of patients who were not receiving therapy. The effect on renal blood flow was similar. The plasma concentrations of sodium and potassium were not altered. Therefore, we conclude that prolonged administration of reserpine did not have a significant effect on renal blood flow, glomerular filtration rate, or plasma electrolytes.

OBSERVATIONS ON THE ENDOCRINE SYSTEMS

Our observations indicate that Rauwolfia (whole root and alseroxylon fraction) does not depress the thyroid after six weeks to three months of drug administration to hypertensive patients. However, Winsor [15] has obesrved a slight depression in basal metabolic rates following reserpine administration. Whether or not there is a difference in response to the different compounds studied has not been determined. However, there was no effect on I^{131} uptake in 10 hypertensive patients (observed by me) who received Rauwolfia for six weeks or more. Therefore, it seems quite likely that if the basal metabolic rate is actually depressed after reserpine administration this may be a short-term response, which is not present after two to three months of continuous administration of the Rauwolfia alkaloids, or it may be a response not mediated by the thyroid.

Winsor [15] has observed that reserpine does not alter the adrenal cortex response to corticotropin. Gaunt and co-workers [18] have observed a slight increase in adrenal cortex metabolites but concluded that this was a nonspecific response similar to that seen with many other drugs.

Gaunt and co-workers [18] have also observed an acute and maintained reduction in urine output in rats following the initial and continuous administration of reserpine. This was followed by a spontaneous decrease in water intake, which was attributed to possible release of antidiuretic hormone. However, we have observed a similar response in patients with hypertension on whom renal-function studies were done simultaneously. Usually the decrease in water excretion was associated with a reduction in glomerular filtration rate, suggesting that tubular reabsorption did not decrease concurrently with the reduction in glomerular filtration rate and as a result urine volume and sodium excretion decreased. However, the latter were short-term observations and may not be comparable to observations made over periods of days to weeks.

The effect of reserpine on experimental hypertension produced by giving desoxycorticosterone acetate (DCA) and salt to rats is of interest. In the studies of Gaunt and co-workers[18] of rats treated with desoxycorticosterone acetate and salt, two-thirds of the animals died within three months with a malignant hypertension syndrome. Reserpine and hydralazine when given alone were only slightly effective in reducing the death rate; however, when given in combination they were universally successful in preventing the hypertension, and none of the animals died. On the contrary, reserpine when given alone was effective in controlling the hypertension produced by chronic cortisone administration. Therefore, these agents are effective in controlling experimental hypertension of humoral origin and preventing death in these animals.

SUMMARY

The pharmacodynamics of administration of Rauwolfia compounds to laboratory animals and patients with hypertension are reviewed. There is no experimental evidence available to indicate that Rauwolfia extracts which are available for clinical use differ qualitatively in their pharmacological activity. Apparently they reduce the blood pressure both in laboratory animals and in patients with hypertension by central sup-

pression of vasoconstrictor impulses, thus decreasing the outflow of vasoconstrictor impulses over the sympathetic nervous system to the arterioles.

The reduction in blood pressure is primarily due to peripheral vasodilatation, since cardiac output is not altered significantly, even though the heart rate usually decreases.

The drug is a sedative which decreases anxiety with a minimum amount of soporific effect. This response is usually lost after two to three months of continuous drug administration and in a small percentage may actually be replaced by anxiety and insomnia due to the drug.

There is very little effect on renal hemodynamics in laboratory animals. In patients with hypertension, glomerular filtration rate is slightly reduced as the blood pressure decreases following parenteral administration of reserpine, but after chronic oral administration no consistent effect has been seen.

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Drug Therapy (Rauwolfia) of Hypertension

II. A Comparative Study of Different Extracts of Rauwolfia When Each Is Used Alone (Orally) for Therapy of Ambulatory Patients with Hypertension

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Rauwolfia has been used for many years in India for treating hypertension, nervous disorders, and as a sedative.[1] Since the introduction of the first Rauwolfia serpentina preparation to American clinics,* a large number of Rauwolfia derivatives have been investigated regarding effectiveness in treating arterial hypertension. A standardized alkaloidal extract (alseroxylon) was introduced into this country in 1952.[4] Since this time, a number of other preparations have been made available, including at least two isolated active alkaloids, reserpine[6] and rescinnamine.[7]

Although the Rauwolfia bibliography is quite large, there have been relatively few reported studies in which the efficacy of the various derivatives of Rauwolfia have been compared. This report is a comparative study of Rauwolfia in treating hypertension and has two major objectives, (1) to compare the clinical results obtained with single, pure alkaloids of Rauwolfia serpentina (e. g., reserpine and rescinnamine) and those obtained with preparations containing multiple active alkaloids (e. g., alseroxylon, Roxinil, or whole root) and (2) to determine, if possible, the type of case for which these agents are particularly suited. A future report will deal with results obtained when Rauwolfia extracts are combined with other antihypertensive agents. We have made no attempt to compare our results with those obtained in other investigational centers. Such comparisons are valid only when the methods and materials used are similar.

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* References 2 and 3.

MATERIALS AND METHODS

The patients used in this study were obtained through three channels and represent three categories of hypertensive patients, patients from (1) the Cardiac Clinic of the Jefferson Davis Hospital (City-County Hospital), (2) the Veteran's Administration Hospital, and (3) our private practice. A total of 346 cases of hypertensive vascular disease are included. Most of the patients were treated as outpatients. They were observed for from one to three months (control period) before treatment. All patients had careful preliminary history and physical examinations, complete blood cell counts, urinalyses, blood urea nitrogen and phenolsulfonphthalein tests, Fishberg concentration tests, chest roentgenograms, and electrocardiograms. These were repeated at regular intervals.†

The criterion for inclusion in the study was an average control blood pressure greater than 150/100. All patients received placebos during the control period. If the systolic or diastolic pressure decreased below this level under placebo therapy, the patient was automatically discarded from the study. The criteria for responsiveness to drug therapy was a fall of at least 20 mm. Hg in the average upright mean blood pressure, or a fall below 150/100 mm. Hg, which was considered the normotensive level.

In each case the control blood pressure represents the average of at least eight pretreatment determinations. The control as well as the follow-up determinations of the blood pressure were taken in both the supine and upright positions at the time of each semiweekly or weekly visit to the clinic. In addition to the blood pressure, the pulse rate, weight, symp-

† Observations were repeated at intervals of one to three months, depending on responsiveness or unresponsiveness of the patient.

TABLE 1.—*Incidence of Complications Associated with Hypertensive Vascular Disease Prior to Treatment with One of the Rauwolfia Compounds*

	Groups	Subgroup A, Control Diastolic Pressure > 100 but < 120 Mm. Hg		Subgroup B, Control Diastolic Pressure > 120 Mm. Hg		Total (Subgroups A & B)	
		No.	%	No.	%	No.	%
Total patients treated							
Roxinil	1	27	100	13	100	40	100
Alseroxylon	2	69	100	49	100	118	100
Rauwolfia (crude root)	3	21	100	21	100	42	100
Reserpine	4	28	100	34	100	62	100
Rescinnamine	5	42	100	42	100	84	100
Complications							
Heart failure							
Roxinil	1	9	33	9	69	18	45
Alseroxylon	2	34	49	25	51	59	50
Rauwolfia (crude root)	3	6	29	10	48	16	38
Reserpine	4	4	14	9	26	13	21
Rescinnamine	5	7	17	15	36	22	26
Abnormal electrocardiogram							
Roxinil	1	12	44	8	62	20	50
Alseroxylon	2	28	41	35	71	63	53
Rauwolfia (crude root)	3	8	38	16	76	24	57
Reserpine	4	14	50	23	68	37	60
Rescinnamine	5	30	71	34	81	64	76
Angina pectoris							
Roxinil	1	4	15	3	23	7	18
Alseroxylon	2	7	10	8	16	15	13
Rauwolfia (crude root)	3	3	14	6	29	9	21
Reserpine	4	1	4	1	3	2	3
Rescinnamine	5	7	17	5	12	12	14
Eye-ground changes (3+ or 4+)							
Roxinil	1	..	...	4	31	4	10
Alseroxylon	2	4	6	7	14	11	9
Rauwolfia (crude root)	3	2	10	6	29	8	19
Reserpine	4	2	7	9	26	11	18
Rescinnamine	5	1	2	3	7	4	5
Renal damage							
Roxinil	1	2	7	7	54	9	23
Alseroxylon	2	10	14	10	20	20	17
Rauwolfia (crude root)	3	3	14	6	29	9	21
Reserpine	4	1	4	5	15	6	10
Rescinnamine	5	4	10	17	40	21	25
Cerebrovascular disease							
Roxinil	1	4	15	8	62	12	30
Alseroxylon	2	16	23	18	37	34	29
Rauwolfia (crude root)	3	4	19	9	43	13	31
Reserpine	4	4	14	7	21	11	18
Rescinnamine	5	10	24	18	43	28	33

toms, and a brief physical examination were recorded at each clinic visit.

The post-treatment blood pressure in each case is an average of all recordings made after the first six weeks of treatment with one of the Rauwolfia preparations. For the purpose of analysis, the patients were divided into five groups according to the drug that they received. The patients receiving any one drug were again divided into two subgroups according to their diastolic blood pressure levels. Patients with less severe hypertension, in whom the average diastolic blood pressure during the control period was more than 100 mm. Hg but less than 120 mm. Hg, were included in Subgroup A. Subgroup B consisted of patients in whom the control diastolic pressure was greater than 120 mm. Hg. These latter patients represent the group with the severest and most advanced degree of hypertensive disease and those in whom the incidence of complications before treatment was high. The compounds studied were Roxinil ‡ (Group 1) and alseroxylon § (Group 2) (purified extracts containing multiple alkaloids); crude Rauwolfia (the whole root)

‡ Supplied by Sharp & Dohme, Division of Merck & Co., Inc.[5]

§ Supplied by Riker Laboratories, Inc., as Rauwiloid.

(Group 3), and reserpine (Group 4) and rescinnamine (Group 5), both isolated active alkaloids. Table 1 summarizes the patients and the incidence of pretreatment complications due to hypertensive vascular disease for each group of patients studied.

The type of patients, the severity of disease, and the over-all incidence of complications are more or less comparable for all of the groups.

Analysis of Patient Material According to Drug Received (Groups 1 to 5)

Roxinil (Group 1).‖—Group 1 consisted of 40 patients with hypertensive vascular disease who received Roxinil. These patients were subdivided further into Subgroups 1A and 1B according to their control diastolic pressure, as noted above. After the control period, 25 patients received 20 mg. of Roxinil per day and 15 received 40 mg. per day. The drug was given in divided doses three times daily. When the results were analyzed with respect to dosage,[5] a difference in response was not seen. Therefore, in the current report no differentiation is made with respect to dosage in this group of patients. The group included 26 Negro and 14 white patients, 18 men and 22 women. The average age was 48 years, with a range of 33 to 71 years.

The severity of the disease is best illustrated by the high incidence of complications. Heart failure was present in about one-half of the patients. This was commoner in the patients with diastolic pressures in excess of 120 mm. Hg. About one-half of the patients had abnormal electrocardiograms. Nine patients showed myocardial ischemia and residuals of previous infarctions and the remaining 11 patients had left ventricular hypertrophy.

About one-third of the patients had evidence of cerebrovascular damage. Four of the patients presented a previous history of cerebrovascular accidents. Retinal hemorrhages were present in four patients.

Alseroxylon (Group 2).¶—This group consisted of 118 patients. There were 41 Negro and 77 white patients, 56 men and 62 women. The average age was 52 years, with a range of 26 to 80 years. The high incidence of pretreatment complications (summarized in Table 1) is indicative of the severity of disease in these patients. About one-half of the patients exhibited varying degrees of heart failure. One-half of the patients had abnormal electrocardiograms. About one-fifth had evidence of renal damage, and about one-third exhibited evidence of cerebrovascular damage.

The 118 patients in this group were all started on alseroxylon, 2 mg. four times daily. In order to determine maximum effectiveness the dose was increased progressively at biweekly intervals until a dose of 16 to 24 mg. daily was being administered. In a few cases, the dose was increased to from 32 40 mg. daily. No greater incidence in either side-effects or blood pressure reduction was encountered when the dose was increased above 8 mg. (4 tablets) per day. Since no advantages were seen from larger doses, 8 mg. daily was selected as the standard dose. Our current data seem to indicate that 8 mg. daily is adequate and that little additional response is obtained with larger doses.#

Rauwolfia (Whole Root) * (Group 3).—Whole root (Rauwolfia) was given to 42 patients; 21 were men, and 21 were women; 23 were Negro, and 19 were white. The average age was 49 years, with a range of 30 to 78 years. The incidence of complications was high (Table 1), as with patients in the groups receiving the other Rauwolfia preparations. About one-third of the patients had heart failure; one-third had evidence of cerebrovascular involvement, and one-fifth had evidence of renal damage.

One-half of the patients were given 50 mg. four times a day initially, and the other half were given 100 mg. four times a day. The doses were later increased gradually † to determine maximum effectiveness. A maximum dose of 2000 mg. (500 mg. given four times a day) was administered. Doses exceeding 500 mg. per day did not increase the response rate. The majority of the patients who responded to 500 mg. per day also responded to doses of 150 to 200 mg. per day, although an occasional patient responded to the larger dose who did not respond to the smaller dose. Therefore, a maintenance dose of 500 mg. per day was employed on all of the patients as a standard maintenance dose unless the severity of side-reactions prevented this. It was concluded that 500 mg. per day was the maximally effective dosage.

‖ According to the manufacturer, Roxinil is an extract containing multiple alkaloids of both reserpine-like and serpentine-like material; furnished by Sharp & Dohme, Division of Merck & Co., Inc.

¶ This is a standardized alkaloidal extract containing reserpine, rescinnamine, and other hypotensively active alkaloids which are not yet characterized.

The dose titration was carried out in this group since these patients were studied early in our experience with Rauwolfia and it was not known then that a maximum effective dose existed for Rauwolfia compounds, beyond which further reduction in blood pressure could not be anticipated.

* This is an unrefined whole root preparation containing all of the alkaloids, furnished by Riker Laboratories as Prep. 1043 and by E. R. Squibb & Sons as Raudixin.

† The dose titration was carried out in this group since these patients were studied early in our experience with Rauwolfia and it was not known then that a maximum effective dose existed for Rauwolfia, beyond which a further reduction in blood pressure could not be anticipated.

Reserpine (Group 4).‡—A group of 62 ambulatory patients with mild to severe hypertension were treated with oral reserpine. When the patients were divided into two subgroups according to the level of diastolic blood pressure, Subgroup 4B consisted of 34 patients with severer hypertension, in whom the average diastolic pressure during the control period was more than 120 mg. Hg and Subgroup 4A consisted of 28 patients in whom the diastolic pressure was more than 100 but less than 120 mg. Hg.

There were 35 women and 27 men, with ages ranging from 27 to 79, with a mean of 53 years. Approximately 10% had evidence of renal impairment, which was severe in only three cases. The cardiac complications were mild in most of the patients. Approximately one-fifth of the patients had developed congestive heart failure at some time prior to therapy, but this was severe in only four patients. Two patients complained of chest pain which was typical of angina pectoris, and one had a history of a myocardial infarction. The electrocardiograms during the control periods were abnormal in 37 patients. In 28 of these there was evidence of left ventricular hypertrophy, and in the remaining 9 frank myocardial damage was evident.

Cerebrovascular disease was present in approximately one-fifth of the patients. This was evidenced by a history of previous cerebrovascular accidents, with varying degrees of residual impairment. Hypertensive encephalopathic manifestations were present in only one case. Eye-ground changes varied from Grades 1 to 3 (Keith-Wagener classification). Eleven patients presented retinal hemorrhages.

After the control period oral reserpine was started, in doses of 1 to 2 mg. per day, in divided doses, after each meal and at bedtime. If excessive sedation occurred, the dose was decreased temporarily, and after several weeks it was increased again to the previous level. If no reduction in blood pressure was observed after two weeks, the dose of reserpine was increased progressively until 1.5 mg. was given four times daily (total, 6.0 mg. daily), in order to obtain maximum effectiveness. As in the previous studies, these rather large doses were given because the side-effects were neither serious nor incapacitating and excessive hypotension was not observed. It was found that doses in excess of 2 mg. per day did not increase the response rate. Some patients were maintained as well on doses of 0.5 to 1 mg. per day as on 2.0 mg., but the over-all response rate was lower with doses under 2.0 mg. per day.

‡ Reserpine is a single alkaloid extracted from Rauwolfia, furnished as Serpiloid by Riker Laboratories and as Serpasil by Ciba Pharmaceutical Products, Inc.

Rescinnamine (Group 5).§—Eighty-four patients with mild to severe hypertension received rescinnamine. These patients were also divided into two subgroups. Subgroup 5B contained 42 patients with control diastolic pressures in excess of 120 mm. Hg, and Subgroup 5A contained 42 patients with diastolic pressures less than 120 mm. Hg. There were 44 women and 40 men; 54 were Negro, and 30 were white. The average age was 50 years, with a range of 30 to 72 years. Approximately one-fourth of the patients had clinical evidence of heart failure; one-fourth had renal damage, and one-third showed clinical evidence of cerebrovascular changes. Three-fourths of the group manifested electrocardiographic abnormalities.

After control observations the patients received 0.5 mg. of rescinnamine four times a day (total of 2 mg. per day) for two months. The dose was then increased to 4 mg. per day for an additional two months or more to determine whether the response rate could be increased with higher dosage. It was found that increasing the dose increased the response rate only slightly. When doses less than 2 mg. per day were used, a maximum incidence of response could not be maintained.

RESULTS

A summary of results with all of the Rauwolfia extracts used is presented in Table 2. In general, the response rate was comparable for all the products. Furthermore, the percentage of patients obtaining a significant reduction in blood pressure (mean pressure reduced more than 20 mm. Hg) was similar in the two subgroups, i. e., diastolic blood pressure <120 as compared with those with diastolic pressure >120 mm. Hg. The severity of the disease did not alter the response rate. However, the percentage of patients who became normotensive (pressure maintained below 150/100) was significantly higher in the group with less severe disease. This was generally true regardless of the Rauwolfia extract employed.

Roxinil (Group 1).—Of the 27 patients with diastolic pressures above 100 mm. Hg but less than 120 mm. Hg (Subgroup 1A), 18 (67%) showed a significant blood pressure reduction, i. e., the mean pressure was reduced in excess of 20 mm. Hg. This compares with a response rate of 8 (62%) of 13

§ Single alkaloid from Rauwolfia, furnished by Riker Laboratories, Inc.

TABLE 2.—*Blood Pressure Response to Different Extracts of Rauwolfia*

Drug	Control Diastolic < 120 Mm. Hg but > 100 Mm. Hg (Subgroup A)					Control Diastolic > 120 Mm. Hg (Subgroup B)					Totals (Subgroups A & B)				
	Number Treated	Responsive		Normotensive		Number Treated	Responsive		Normotensive		Number Treated	Responsive		Normotensive	
		No.	% *	No.	% †		No.	% *	No.	% †		No.	% *	No.	% †
Roxiall (Group 1)	27	18	67	13	48	13	8	62	2	15	40	26	65	15	38
Alseroxylon (Group 2)	69	34	49	30	43	49	26	53	12	24	118	60	51	42	36
Rauwolfia (Group 3)	21	11	52	6	29	21	12	57	3	14	42	23	55	9	21
Reserpine (Group 4)	28	13	46	9	32	34	20	59	2	6	62	33	53	11	18
Reselnnamine (Group 5)	42	19	45	8	19	42	21	50	3	7	84	40	48	11	13
	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Totals and per cent	187	95	51	66	35	159	87	55	22	14	346	182	53	88	25

* Per cent of patients in this subgroup who obtained a reduction in mean blood pressure of 20 Mm. Hg or more from control value.
† Per cent of patients in each subgroup who became normotensive (blood pressure < 150/100).

patients with control diastolic pressures in excess of 120 mm. Hg. Therefore, the rate of responsiveness does not seem to be dependent on the severity of the hypertension prior to therapy. However, 13 (48%) of the patients from Subgroup 1A, with less severe hypertension, became normotensive (blood pressure less than 150/100 mm. Hg), whereas only 2 (15%) of the patients in Subgroup 1B, with severer disease, became normotensive. Patients with heart failure and renal damage seemed to be particularly resistant to therapy. Seventy per cent of the patients showed a reduction of 10 beats or more in pulse rate. This occurred independently of the blood pressure response.

Alseroxylon (Group 2).—Of the 118 patients receiving alseroxylon, 51% achieved a significant reduction in blood pressure and 36% became normotensive. The response rate was about equal in Subgroup 2A and Subgroup 2B (49% and 53%, respectively); thus severity of disease did not effect responsiveness. However, 43% of the patients with control diastolic pressures less than 120 mm. Hg (Subgroup 2A) became normotensive, as compared with 24% of the patients with control diastolic pressures above 120 mm. Hg. Sixty-five per cent of the patients obtained a reduction of 10 or more beats in pulse rate. It is noteworthy that despite the absence of blood pressure reduction in the unresponsive group there was a slowing of the pulse rate from an average control rate of 82 to 67 beats per minute.

There was a high incidence of complications, due to hypertension, in the unresponsive patients. This would indicate that the patients with less severe hypertension with no complications are more likely to show a satisfactory effect from alseroxylon. However, it is not entirely necessary that complications be absent for satisfactory results to be seen.

Rauwolfia (Whole Root) (Group 3).—Forty-two patients received the whole root of Rauwolfia. Fifty-five per cent obtained a significant reduction in blood pressure, and 21% became normotensive. As with the alkaloidal extracts, the patients who became

normotensive were predominantly those with less severe disease in Subgroup 3A (29% in Subgroup 3A as compared with 14% in Subgroup 3B). A reduction in pulse rate (due to the drug) of 10 beats per minute or more was observed in 74% of the patients receiving whole root.

Reserpine (Group 4).—Fifty-three per cent of the patients receiving reserpine showed a significant reduction in blood pressure. The incidence of blood pressure response was not increased significantly when treatment was prolonged beyond two to three months. Eighteen per cent of the patients were rendered normotensive (less than 150/100 mm. Hg). Percentage-wise, a few more patients with diastolic pressures above 120 mm. Hg responded (59%) compared with those with diastolic pressure between 100 and 120 mm. Hg (46%). However, with the exception of two cases, a reduction in blood pressure to normotensive levels was obtained only in the patients with less severe disease. The patients in this study who presented moderate to marked renal and cerebral impairment were less likely to respond with a satisfactory blood pressure reduction. The pulse rate decreased 10 beats per minute or more in 71% of the patients, which is comparable to the bradycrotic response from extracts containing multiple alkaloids.

Rescinnamine (Group 5).—The response rate of the patients receiving the pure alkaloid rescinnamine was similar to the response rate of the group receiving reserpine. Forty-eight per cent of the entire group of 84 patients obtained a significant reduction in blood pressure, and 13% became normotensive. In Subgroup 5B (control diastolic pressures above 120 mm. Hg) 7% became normotensive, compared with 19% of the patients in Subgroup 5A, with control diastolic pressures less than 120 mm. Hg. Fifty-five per cent obtained a significant reduction in pulse rate, compared with 71% of the patients receiving reserpine. Not only was the incidence of the bradycrotic response less with rescinnamine as compared with reserpine but the degree of reduction in pulse rate was also less. This makes rescinnamine a superior

TABLE 3.—*Analysis of Symptomatic Responses to Different Rauwolfia Preparations*

Symptom	Roxitil			Alseroxylon			Rauwolfia (Whole Root)			Reserpine			Rescinnamine		
	Number Complaining	Improved		Number Complaining	Improved		Number Complaining	Improved		Number Complaining	Improved		Number Complaining	Improved	
		No.	%		No.	%		No.	%		No.	%		No.	%
Headache	14	6	43	69	52	75	16	11	69	32	16	73	21	15	71
Angina pectoris	7	2	29	15	7	47	9	2	22	2	1	50	12	5	42
Congestive heart failure	18	2	11	59	8	14	16	2	13	13	2	15	22	7	32
Electrocardiogram	20	1	5	63	5	8	24	2	8	37	2	5	64	4	6
Fundi	4	0	..	11	1	9	8	0	..	11	0	..	4	1	25
Renal impairment	9	0	..	20	0	..	9	0	..	6	0	..	21	0	..
Hypertension	40	26	65	118	60	51	42	23	55	62	33	53	84	40	48

drug for the exceptional patient who develops severe bradycardia with reserpine. For example, we have observed a number of patients in whom the pulse rate dropped below 50 while they were receiving reserpine and, in one, it decreased to 38 beats per minute and remained there for three days after the reserpine was discontinued.

COMMENT

General Comment.—One-third to one-half of the patients reported an improved sense of well-being while receiving any of these compounds. Headaches were benefited in about three-fourths of the patients in whom this symptom was a major complaint prior to therapy. Cardiac failure improved significantly in a number of instances without change in therapy other than the administration of one of the Rauwolfia extracts.

Side-Actions.—Extracts with Multiple Alkaloids (Roxinil, Alseroxylon, and Rauwolfia [Whole Root]): Side-actions to Roxinil, alseroxylon, and whole root therapy are presented in Table 4. There was very little difference among the three compounds. The most frequent complaint was nasal congestion, which was experienced by from one-half to three-fourths of the patients. This was usually intermittent and was worse at night. It was severe and sufficiently distressing in several instances to necessitate discontinuance of the drug. Antihistaminics were used in an attempt to avoid this complaint, but, even when they were effective, the response was temporary. Vasoconstrictor nose drops, used as infrequently as possible, seemed to be the best method for combating this complaint. However, if used too frequently, these became ineffective after two or three weeks. Phenylephrine (Neo-Synephrine) seemed to be the most effective agent.

Sedation was a prominent symptom in about half of the patients. However, this was most prominent during the first two or three weeks of therapy. It decreased with time and by the third month it had become minimal in most instances. In some of the patients, sedation was followed by insomnia at night. This was rather marked in a few patients.

Increased frequency of bowel movements was observed in the majority of the patients. Usually the stool remained well formed, and diarrhea was observed in less than 10% of the patients. The intestinal stimulant effect appeared to decrease with prolonged therapy in most cases.

Weakness and fatigue were observed in about 40% of the cases receiving Roxinil and necessitated discontinuance of the drug in three patients. It was less marked in those patients receiving alseroxylon or the whole root. In general, weakness following medication with these agents was not as severe as it was during the administration of reserpine. Dizziness, unrelated to excessive hypotension, was observed in about one-fourth of the patients receiving Roxinil, but it was seen in only 7% of the patients receiving alseroxylon and 10% of the patients receiving the whole root. Both dizziness and weakness improved as therapy was continued. Nightmares and other complaints were occasionally observed, but these were too infrequent to be of major significance.

Single Alkaloids (Reserpine and Rescinnamine): Sedation was a prominent accompaniment of reserpine therapy. The degree of sedation (but not the incidence) was more marked following reserpine administration than it was following the administration of the extracts containing multiple alkaloids. A number of the patients who complained previously of nervousness and irritability became calmer and more tranquil (Table 4). On the other hand, some of the patients complained bitterly of a letdown feeling and a sense of weakness. Tolerance to the sedative effect was the rule in patients who received the drug for prolonged periods of time, although a number of patients continued to complain of weakness even after periods of three to four months. Patients who complained of somnolence soon after initiation of therapy were often relieved of this complaint after several weeks, frequently without reducing the dosage. However, as a rule, when excessive somnolence developed on the initial dose we reduced the dose for a week or two. Although the incidence of

sedation in patients receiving reserpine and rescinnamine did not differ greatly (47% as compared with 35%), the degree of somnolence was much less in the patients receiving rescinnamine, compared with those receiving reserpine.

The incidence and intensity of the bradycrotic response were more marked with reserpine than with rescinnamine, the incidence with reserpine being about equivalent to that with the preparations containing multiple alkaloids. Nasal congestion was also less marked during the administration of rescinnamine than during reserpine administration. A few patients complained of muscle aches and pains during the initiation of reserpine therapy, but this was usually temporary.

Psychogenic Anxiety, Depressive Reactions: Depression accompanied by anxiety was observed in a number of patients receiving reserpine. This was the most serious side-reaction that we have observed. It was not seen during the administration of rescinnamine, and it has been very infrequent during the administration of either crude Rauwolfia or alseroxylon. One patient developed this complication while receiving Roxinil. The clinical picture was quite typical. The patients were characteristically restless and depressed, with a pronounced sense of panic and impending danger. Patients who previously were meticulous and neat about their person became careless and lost interest in their appearance. They invariably contacted the attending physician innumerable times to discuss their problems and depressed feelings. They were resistant to reassurance. Insomnia became severe and was frequently unresponsive to sedatives. We treated one patient who required 600 mg. of pentobarbital at night before she could go to sleep, though previously she had never been troubled with insomnia. Two typical patient histories are presented.

TABLE 4.—*Summary of Pharmacodynamic Responses (Beneficial and Untoward) to Different Extracts of Rauwolfia*

	Roxinil		Alseroxylon		Rauwolfia (Whole Root)		Reserpine		Rescinnamine	
	No.*	% †	No.*	% †	No.*	% †	No.*	% †	No.*	% †
Total number treated	40	100	118	100	42	100	62	100	84	100
Side-effect										
Beneficial										
Blood pressure reduction	26	65	60	51	23	55	33	53	40	48
Bradycrotic response	28	70	77	65	31	74	44	71	46	55
Sedation	20	50	63	53	24	57	29	47	29	35
Sense of well-being	16	40	67	57	21	50	22	35	23	27
Untoward										
Nasal congestion	22	55	85	72	31	74	40	65	43	51
Diarrhea	5	13	7	6	3	7	3	5	6	7
Increased appetite	24	60	72	61	26	62	37	60	28	33
Weight gain	19	48	73	62	22	52	31	50	34	40
Fatigue and weakness	16	40	13	11	10	24	27	44	13	15
Dizziness	12	30	8	7	4	10	13	21	4	5
Nightmares	4	10	7	6	3	7	4	6	3	4
Dysuria	1	3	2	2	1	2	1	2	0	..
Impotence	2	5	1	1	1	2	2	3	0	..
Syncope	0	..	0	..	0	..	1	2	1	1
Muscular aches	3	8	1	1	2	5	6	10	0	..

* Number of patients showing this particular response to the specific drug.
† Patients presenting side-effect expressed as per cent of total number of patients treated with this particular drug.

CASE 1.—A 38-year-old male physician, employed in academic medicine, described his own case history. He is now completely recovered, leading a normal academic life as full professor in a medical school. His response is reported in his own words during recovery from a depressed-anxiety reaction resulting from reserpine therapy. Complete recovery from the effects of reserpine was not seen until three months after the therapy was discontinued.

"The onset of this complicating illness was quite sudden on Nov. 4, 1954, with an intensely uncomfortable feeling of anxiety and apprehension. There was a more or less constant sensation of substernal

aching and oppression which at times was almost painful. As time wore on, it seemed to me that the cause for this apprehensive state was a realization of personal inadequacy and lack of self-confidence. There was a pronounced tendency for self-scrutiny and all past experience was reviewed as having been cumulatively contributory to this sense of inadequacy. Although it seemed true that circumstances had not provided ideal opportunities, I felt I had not made the best use of my time and ability. My approach to work had not always been mature and I had been too willing to gloss over and get by. I had not learned from the medical experience I had had and had not accumulated the special knowledge and accomplishments which would be commensurate with my position and reputation. Self-criticism and deprecation were extreme and seemed justified. I was disturbed over not having details of matters which came up during rounds and medical conferences and particularly over having forgotten much of what I had known. My powers of observations and retention were inadequate, and I felt mentally sluggish and distractible. I became fearful and reluctant to accept responsibility for patient care, feeling that I could not do an adequate job, in spite of the fact that at the moment I was apparently capably handling seriously ill patients. Every comparison I made of myself with others was unfavorable to me. It seemed I knew very little more than our resident staff. I began consulting textbooks and the literature to check on myself, etc. Anything that was complex or difficult became very burdensome. I analyzed myself as lacking initiative, drive and energy for sustained and organized work.

"Sleep at first was exceedingly difficult. Sedation at night was necessary for about ten days to two weeks, after which I learned to sleep fairly well. Chlorpromazine was begun by a consulting psychiatrist and doses up to 50 mg. four times a day seemed of little or no benefit, as far as I could determine. The addition of Dexedrine [dextroamphetamine] was tried for several days and was of considerable help in that I tended less to dwell on my deficiencies. However, I could not tolerate the drug because of the severe insomnia it induced.

"It seemed to me that the reserpine probably released or 'opened up a Pandora's box' of anxieties. I have always been somewhat perfectionistic, rigid, and obsessive. Much of the anxiety was undoubtedly engendered by the combination of a very heavy clinical load and the urgency of keeping up with my research commitments.

"During the height of this episode, a period of about three weeks, I was certain that reserpine had had only a conditioning effect. During the ensuing few weeks I gradually improved but with considerable waxing and waning. About nine weeks after onset, there seemed to be a sudden and complete remission which lasted for about ten days. With the sudden, but transitory, recovery, I was a little more willing to accept the toxic role of reserpine."

Two weeks after the patient recorded this personal history and three months after reserpine therapy was stopped, he was completely recovered. He had recovered the usual jovial, self-confident, and self-reliant personality which was his before reserpine therapy was instituted. He has now gained complete insight into the origin of his illness, and he completely accepts this experience as a reaction to the drug, although he was unwilling to do so while he had symptoms. He has since taken rescinnamine for two weeks and alseroxylon for one month without difficulty. More recently, he started taking reserpine again and has not as yet had a recurrence of symptoms.

CASE 2.—A white woman aged 63 had moderately severe hypertension without renal involvement. Her pretreatment diastolic blood pressure was 130 mm. Hg. She was initially given alseroxylon and was subsequently switched to 2.0 mg. of reserpine per day. Because of somnolence the dose was reduced to 0.5 mg. and was never subsequently increased above this level. Pentolinium tartrate in doses of 20 mg. was given in addition to the reserpine each morning and evening. On this regimen her blood pressure was maintained constantly between 150 and 180 systolic and 90 to 105 diastolic for a period of four months. Suddenly she was unable to sleep at night, and her reactions as described in her own words follow:

"In 1953 my doctor discovered I had high blood pressure for which I took some brown tablets (alseroxylon) three times a day. The very first medicine helped me. I hardly ever had to take anything for sleeping. After taking the medicine for quite some time my doctor had me go to the hospital for a few days for a general check-up and found my health generally good. At this time the brown tablets (alseroxylon) were discontinued and I started to take some white tablets (reserpine).

"I did quite well after discharge from the hospital for about four months. Then suddenly I became very nervous and upset. I was unable to sleep at night. I worried about my Sunday school and my family. I worried about the dissatisfaction of others as much as myself and became obsessed with this problem. I did not eat or sleep well and unknowingly it brought on nervousness. I went to my doctor because I was so nervous. I worried if my doctor would be 'mad' at me for being so nervous, if I would ever get well, if I had enough faith, even if I was eating the right food. I was so tense and rigid from loss of sleep and not eating that my stomach would roll. My doctor finally sent me to the hospital with instructions for no visitors, even only short visits from my husband. There I finally

slept and was able to eat more and relaxed so I got rid of my nervous stomach. I read three of Vincent Peale's Books, 'Art of Real Living,' 'Guide to Confident Living,' 'Power of Positive Thinking.' I then read a book by Dale Carnegie, 'How to Stop Worrying and Start Living,' which didn't seem to help me. I worried about having to take sleeping pills. After seeing my doctor the last time and being told to write down all my worries and all about my present problems, I was upset and did not sleep the first night. I then tried taking walks and deep breathing exercises in an effort to improve my appetite. I hope with this information, with the medicines, by my doctor's good services, the help of God, my prayers and good thinking I trust that I will be able to relax and stop worrying and start living again so I can enjoy life again."

Reserpine was discontinued when this patient was admitted to the hospital. After two weeks her symptoms improved enough so that she could be discharged. The patient was then given methylphenyl (2-piperidyl) acetate-hydrochloride (Ritalin ‖), and after 48 hours she was completely free of symptoms. Ritalin was discontinued after one week and the patient has now been symptom-free for three months. She sleeps well without the aid of sedatives, whereas during the height of the reaction to reserpine she required as much as 400 mg. of pentobarbital to induce sleep.

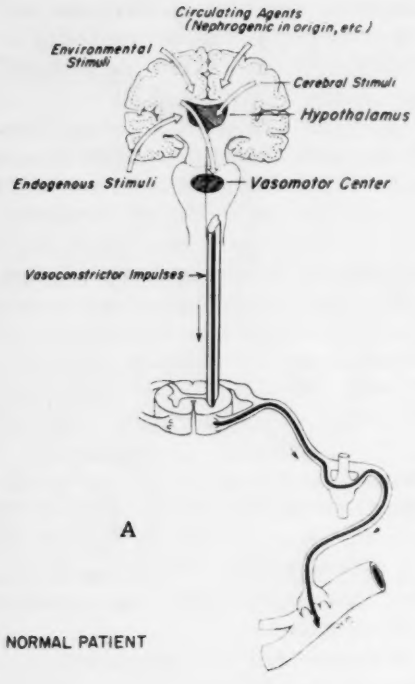
The symptoms of acute anxiety in the previous two cases were undoubtedly due to reserpine. They are presented in detail because the manifestations can be insidious and may so closely resemble the anxiety manifestations frequently associated with hypertension that the physician may not recognize them as part of an unfavorable reaction to the drug. Nevertheless, they can be sufficiently serious that suicide is a distinct possibility. We have observed one patient who attempted suicide, although there had been no previous suggestion of such a reaction. She has not made similar attempts since discontinuing the drug, and her period of follow-up is now in excess of one year.

COMMENT

It seems evident from the data presented that an extract of Rauwolfia serpentina, when administered as the sole therapeutic agent, provides a safe and relatively effective treatment for mild uncomplicated hypertensive vascular disease. In the milder cases, up to 50% of the patients may be expected to show a satisfactory reduction in blood pressure. A much smaller percentage of the severe cases will manifest satisfactory lowering of blood pressure with Rauwolfia extracts alone, although such a response will be seen in some patients. For the remainder, Rauwolfia is the background agent upon which may be superimposed adjunctive therapeutic agents such as hydralazine (Apresoline), veratrum (Veriloid), a ganglionic blocking agent (hexamethonium, pentolinium tartrate [Ansolysen], or meborylamine hydrochloride [N-methyl-dl-isobomylamine hydrochloride]) or adrenergic blocking agents (N-phenoxyisopropyl-N-benzyl-β-chloroethylamine hydrochloride [Dibenzyline]). When these are added to Rauwolfia, they are effective in smaller doses and the side-effects to these more potent agents are correspondingly reduced.

It is noteworthy that patients with severer hypertension, who stand to gain most from treatment with antihypertensive agents, are less likely to respond adequately to Rauwolfia extracts alone. On the other hand, the fact that Rauwolfia preparations are relatively free from serious side-effects and rarely produce an excessive reduction in blood pressure makes them safe for use in the presence of cardiac, renal, and cerebrovascular complications. Furthermore, these same properties justify the use of Rauwolfia preparations in patients whose disease might otherwise be regarded as too mild to merit specific treatment. Certainly not all patients with mild hypertension proceed to develop severe hypertensive cardiovascular disease. Nevertheless, we cannot escape the fact that all severe cases arise from the group with mild hypertension. We are as yet unable to predict which cases will progress to severe disease. Smirk [9] has concluded that if hypertension reaches a sufficient degree of severity and is sustained for an adequate period of time this in itself is an intermediate cause responsible for the clinical manifestations which are associated with all hypertensive diseases. Therefore, it seems rational to use Rauwolfia ex-

‖ Ciba Pharmaceutical Products, Inc.



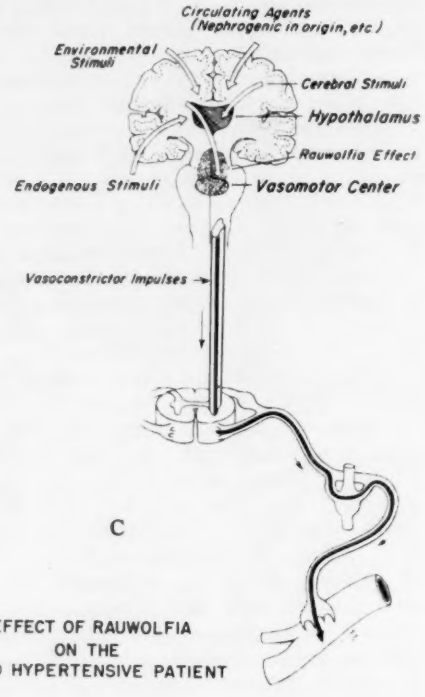


Fig. 1*A*.—Diagrammatic representation of blood pressure regulation by the sympathetic nervous system in a normal person. Vasoregulatory areas in the brain send vasoconstrictor impulses over the sympathetic nervous system to the blood vessels and thus raise the blood pressure by increasing peripheral resistance. Numerous influences such as central stimuli, circulating centrally active agents, emotional and environmental stimuli, reflex stimuli, etc. influence the central vasoregulatory centers and thus lead to alterations in blood pressure.

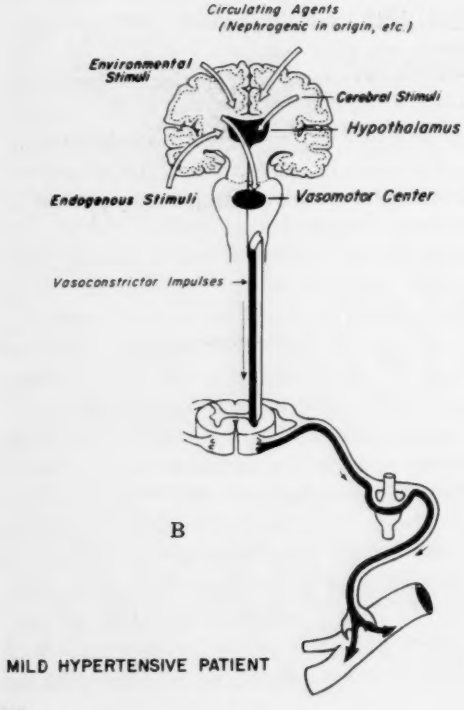


Fig. 1*B*.—Diagrammatic representation of a patient with mild essential hypertension. The various stimuli affecting the vasoregulatory centers in the brain are operative in such a manner as to increase the outflow of vasoconstrictor impulses over the sympathetic nervous system. This leads to an increase in peripheral resistance and the development of the hypertensive state.

Fig. 1*C*.—Diagrammatic representation of the mild hypertensive patient described in Figure 1*B* who is given Rauwolfia. The influences (operative thru the hypothalamus) which previously increased vasomotor activity are now depressed, and the blood pressure returns to normotensive levels; postural reflexes remain intact.

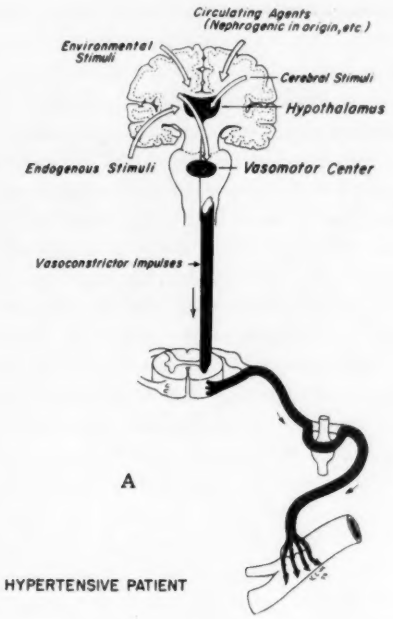


Fig. 2*A*.—Diagrammatic representation of overactivity of vasoconstrictor mechanisms within the sympathetic nervous system in the patient with severe hypertension.

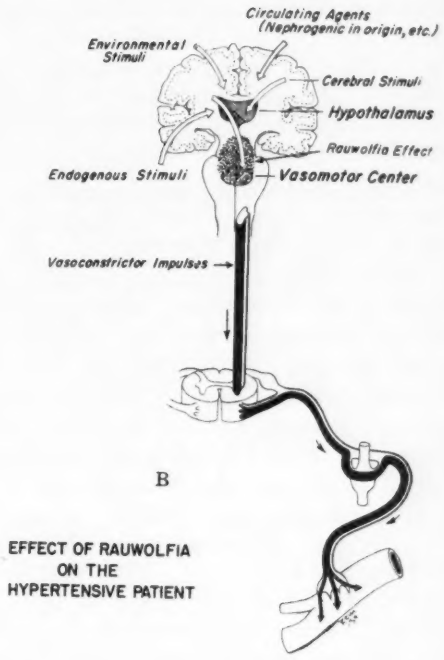


Fig. 2*B*.—When the patient with severe hypertension is given Rauwolfia, vasoconstrictor influences which stimulate the vasomotor areas are depressed just as they are when this drug is given to the mild hypertensive. The blood pressure is reduced moderately, but yet it remains far above normotensive levels. This patient will require adjunctive antihypertensive therapy at a later date.

tracts for the treatment of patients with less severe disease in the hope of preventing progression and the development of serious complications. A family history of hypertension further increases the desirability of early treatment in the mild group.

Whether or not the basic disease process is arrested, it is certainly true that the complications associated with untreated hypertension decrease significantly when the blood pressure is maintained at a lower level. Furthermore, combined therapy, to be described in a future report, provides hope that pathological processes of rapidly progressive disease may be halted or, in many cases, reversed. Schroeder has estimated that the mortality rate would be 4% in a group of patients with essential hypertension who are treated effectively. This is compared with a 40% mortality in untreated patients. In patients with malignant hypertension who are not treated the mortality is 100%, as compared with 10% if these patients are adequately treated.¶

In addition to the lowering of blood pressure, Rauwolfia extracts also produce certain other desirable effects in the patient with hypertension. There is an effect upon the psyche with decrease in tension and aggressiveness which may help those persons make a more satisfactory adjustment to their environment. About one-half of the patients reported a subjective sense of well-being, and this was not necessarily related to a reduction in blood pressure. Hypertensive headaches are relieved in a high percentage of cases when present. In our series, angina pectoris was improved in many patients, particularly when there was preexisting tachycardia and

¶ Schroeder, H., in Panel Discussion before the American College of Physicians, Philadelphia, April 27, 1955.

in those patients who showed a significant fall in blood pressure. Congestive heart failure improved in some cases as a concommitant of reduction in blood pressure. Heart size decreased in some patients with previous cardiac enlargement.

Contrasted with these subjective and objective benefits, there were some side-effects. The most frequent of these was nasal congestion. Though this was nearly as common after long periods of therapy as in the early stages, most patients reported that it had become less severe. Weight gain was seen in approximately one-half of the patients. This seems to be directly related to an increase in appetite. Previous studies have shown that there is no alteration in thyroid function.[4] In several patients the appetite returned promptly to its pretreatment level when the drug was discontinued for a few days. Most of the patients noted some increase in the frequency of bowel movements, but in most cases this was temporary and not sufficiently severe to be called diarrhea. Mild dizziness occurred in 10% to 20% of patients during the first month of therapy. This was not postural and was not necessarily related to a fall in blood pressure. Excessive sedation, weakness, and fatigue were seen with some regularity, but these complaints all tended to decrease as therapy was continued. Although tolerance to the side-effects developed, tolerance to the antihypertensive effects of Rauwolfia preparations did not seem to be a clinical problem.[10] It is true, however, that the maximum hypotensive effect is often seen relatively early in the course of therapy, and the blood pressure ultimately stabilizes at a point slightly above this nadir.

When the several Rauwolfia preparations used in this study are compared, it is apparent that their actions are all qualitatively similar. The hypotensive effect is comparable in degree when optimal doses are used with any of the preparations, whether containing multiple alkaloids or a single alkaloid. All these preparations also seem to produce similar side-effects, and the incidence of the side-effects is not strikingly different with the various preparations. However, the severity of these side-effects does differ. Reserpine produces more weakness, fatigue, and sedation than either rescinnamine or extracts containing multiple alkaloids. In this series reserpine produced mental depression in a number of cases, and this was not observed with rescinnamine and was much less frequent with alseroxylon or the crude root. Although fixed doses of the various preparations were used in the current study for control purposes, when the individual patient (not in a study group) is treated, the maintenance dose should be individualized. In determining the maintenance dose, the therapist should establish the minimum dose which will control the blood pressure equally as well as the larger doses used for initiation of therapy. Although we have not been able to establish a relationship between dose and the incidence and severity of side-reactions, it seems logical that such exists at least to some degree. In establishing the minimumly effective dose, changes in the dose must be made slowly over weeks to months because of the slow onset of action and relatively long cardiovascular response (days to weeks) to the drug.

In comparing the potency of the various preparations, our studies indicate that 1 mg. of reserpine is equivalent in hypotensive activity to 250 mg. of crude root, which is lower than the 1:1000 ratio reported by Wilkins.[8] One milligram of reserpine manifests hypotensive activity equivalent to 4 mg. of alseroxylon. This is consistent with the fact that 4 mg. of alseroxylon contains the active alkaloids extracted from 250 mg. of Rauwolfia serpentina root of average potency. Rescinnamine is slightly less potent than reserpine. All the preparations tested were bradycrotic, but rescinnamine appeared to be somewhat less so than the other preparations. All of the Rauwolfia preparations had a slow onset of action. Reserpine appears to be somewhat more rapid than the other preparations.

SUMMARY AND CONCLUSIONS

Three Rauwolfia preparations containing multiple alkaloids and two representing single

alkaloids have been evaluated clinically for the treatment of hypertension by long-term controlled studies.

There was no significant difference, quantitatively or qualitatively, in the hypotensive action of the five products studied.

The hypotensive activity of 1 mg. of reserpine is estimated to be about equal to that of 250 mg. of crude root, or 4 mg. of alseroxylon.

The side-effects of the five agents were qualitatively similar, but quantitatively there were minor differences, which are discussed.

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Papillary Adenomas of the Colon and Rectum

A Clinical and Pathological Study

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Increasing numbers of patients with mucosal polyps of the rectum and colon are being seen each year at the Lahey Clinic. This is due primarily to the increase in the number of patients being examined by sigmoidoscopy—regardless of symptoms—by us and by our consultants, as a part of every complete physical examination. Since we believe that adenomatous mucosal polyps are true tumors and may undergo malignant change, it follows that tumors of this type should be removed or destroyed when discovered.

Pathologically, we classify epithelial tumors of the colon and rectum as (1) benign mucosal polyps, (2) mucosal polyps with atypical epithelial hyperplasia, (3) mucosal polyps with foci of carcinoma, and (4) carcinoma.

Dr. Shields Warren,[1] in our earlier presentation before this Section of the American Medical Association in 1939, reported that in a series of over 800 cancers of the colon and rectum studied at that time, 12% could be shown to have arisen in preexisting benign mucosal polyps. He was of the opinion that the actual number was much higher but that, because of the destructive nature of the cancer, the original polypoid structure had been destroyed. We have seen carcinoma develop in these regions without apparently progressing through a benign polypoid phase, and we do not believe that all instances of rectal and colonic cancer necessarily originate in a preexisting benign mucosal polyp or that all adenomatous polyps necessarily become cancerous.

From the clinical standpoint, we have long been aware of clinical differences between some of these benign polyps. The papillary adenoma or villous type of polyp has presented peculiarities of location, incidence, development, and clinical course which have differed from other polypoid adenomas. Although we agree with Ewing [2] and Sunderland and Binkley [3] that the villous type of polyp is but a growth variant of the adenoma, we feel that because of certain clinical differences it can be considered a separate clinical entity. For example, almost all villous tumors occur below the rectosigmoid area of the colon. They are of appreciable size when first noted and occur singly. They are found in an older age group than are the usual adenomas or clinical cancers occurring in the colon and rectum. There is general agreement with these observations.

Our treatment of villous polyps of the rectum and colon over the years has been quite conservative; yet the literature in general emphasizes the high incidence of early and localized cancer in these tumors and points out the necessity for radical treatment for the majority. Our experience has been somewhat in contrast to this in that, although we have found an appreciable incidence of localized cancer histologically and a high incidence of local recurrence of these tumors following snare excision and fulguration, no patients have died of metastasizing cancer

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The Lahey Clinic, Department of Surgery (Dr. Swinton) and Fellow in Surgery (Dr. Soland), and New England Deaconess Hospital, Department of Pathology (Dr. Meissner).

TABLE 1.—*Summary of Cases*

Case	Pathological Diagnosis of Greatest Malignancy	Snare Excision and Fulguration, No.	Resection			Years Followed	Status at End of Follow-Up	Remarks
			Excision	Anterior	Miles			
1	Adenocarcinoma	4	..	..	x	7	Well	Fulgurated 4 times in 1 mo.; last biopsy adenocarcinoma; Miles resection
2	Mucosal polyp	15	..	..	..	7	Well	.....
3	Mucosal polyp	8	..	x	..	9	Well	Massive recurrence 8 yr. after last fulguration; ant. resection
4	Mucosal polyp with small focus of carcinoma	5	..	..	..	6	Scarring of rectum	Refused further treatment
5	Mucosal polyp	14	..	..	..	9	Recurrence	Recurred after 9 yr., benign
6	Mucosal polyp	23	..	..	..	9	Recurrence	.....
7	Mucosal polyp, early carcinoma	9	..	..	x	9	Well	Miles after recurrence at 5 yr.
8	Mucosal polyp	2	..	..	..	9	Well	.....
9	Mucosal polyp	12	..	..	..	8	Well	.....
10	Mucosal polyp, early carcinoma	2	..	..	x	6	Dead age 70	Died, coronary, 6 yr. after last treatment, no evidence of carcinoma
11	Mucosal polyp	8	..	..	..	6	Well	.....
12	Mucosal polyp with atypical hyperplasia	6	..	..	..	6	Well	.....
13	Mucosal polyp with atypical hyperplasia	3	..	..	..	7	Well	.....
14	Mucosal polyp	3	..	..	..	7	Well	.....
15	Mucosal polyp with atypical hyperplasia	8	..	..	x	8	Well	Miles resection because of scarring and tendency to recurrence after 2 yr.
16	Adenocarcinoma	..	..	..	x	5	Well	.....
17	Adenocarcinoma	11	x	..	x	6	Well	Fulguration for 1 yr., then excised; had definite carcinoma, and so Miles resection was done
18	Mucosal polyp, early carcinoma	1	x	..	x	5	Well	Recurred 2 yr. after excision; Miles resection because of low level recurrence
19	Mucosal polyp, early carcinoma	3	..	..	..	5	Well	.....
20	Mucosal polyp	20	..	..	x	16	Well	Miles resection for rectal stricture 11 yr. after first treatment
21	Mucosal polyp	5	..	..	..	13	Dead age 79	Died 11 yr. after last treatment
22	Mucosal polyp	1	..	..	..	16	Well	Has had repeated cerebral hemorrhages
23	Mucosal polyp	3	..	..	..	15	Well	.....
24	Mucosal polyp with atypical hyperplasia	..	x	..	..	13	Dead age 69	Died of carcinoma of prostate; no rectal disease
25	Mucosal polyp with atypical hyperplasia	3	..	..	..	10	Well	.....
26	Mucosal polyp	..	x	..	..	13	Well	Age 81, in sanatorium, cerebral arteriosclerosis
27	Mucosal polyp, early carcinoma	..	x	..	..	10	Well	.....
28	Mucosal polyp	..	x	..	..	11	Dead age 75	Died, coronary; no rectal disease
29	Adenocarcinoma	4	..	..	x	18	Well	.....
30	Mucosal polyp with atypical hyperplasia	..	..	..	x	10	Dead age 84	Died, coronary; no rectal disease; Miles resection because of perforation during fulguration
31	Adenocarcinoma	4	x	..	x	6	Well	Miles resection because of recurrence after excision
32	Mucosal polyp	..	x	..	..	5	Dead age 77	Died of reticulum cell sarcoma, stomach; no rectal disease
33	Mucosal polyp with atypical hyperplasia	8	..	..	..	5	Recurrence	.....
34	Mucosal polyp	2	..	..	..	6	Recurrence	.....
35	Mucosal polyp	19	..	x	..	5	Well	Recurred after 2 yr., and so resection was done

and we have not found extension to lymph nodes in our resected specimens.

In an attempt to add to our knowledge of tumors of this type, we have made a study of the 52 patients with villous polyps of the colon and rectum seen at the clinic between the years 1937 and 1950. This number represents 8% of all of the mucosal polyps seen. The records of 35 of these patients, shown in Table 1, were complete in that these patients had been under our personal observation for five or more years. This latter group has been used as the basis for our analysis of the pathology and treatment of these tumors and the end-results. The other 17 patients had incomplete records in that they had gone elsewhere for treatment, had refused treatment, or had died. We cannot prove, at this time, whether any of these 17 patients died of colon or rectal cancer. However, the 35 patients remaining under continuous observation for this extensive period of time do provide us with considerable information on this subject.

Fig. 1.—Villous polyp of the transverse colon.

The clinical entity, papillary adenoma or villous tumor of the colon and rectum, has been adequately and completely described by Sunderland and Binkley,[3] Ewing,[2] Gabriel,[4] Dukes,[5] Bacon,[6] and others,* and, therefore, there is no need in this presentation to describe in detail the gross and histologic anatomy of these tumors.

These tumors vary from those 2 or 3 cm. in diameter to tumors encircling and almost completely filling the entire rectum. They present an irregular flat surface growth projecting into the lumen of the bowel. They tend to be bulkiest toward the center and flattened at the periphery, with suggestive overhanging margins on occasion. Infrequently, a short thick pedicle may be noted, hidden by the overhanging edges. In our experience, this characteristic has been uncommon. Characteristically, these tumors have a wrinkled or folded-over, convoluted appearance. Sometimes they present the appearance of many close-set lobulations. Frequently, the surface is covered by a thick tenacious mucus, and the tumors are often so soft and velvety on palpation of the rectum that an inexperienced observer may not note their presence on first examination. They occur predominantly at the rectosigmoid area of the colon or below. In our series, one tumor was found at the hepatic flexure of the colon; the remainder were within 8 in. of the anal canal. They almost always occur singly. In our series no patient had more than one tumor (Figs. 1 and 2).

MICROSCOPIC PATHOLOGY OF VILLOUS POLYPS

The typical villous polyp or papillary adenoma consists microscopically of an overgrowth of epithelium which is arranged in a single or in a pseudostratified layer over scanty stromal prolongations. The prolongations project outward from the mucosal surface, each individual prolongation seeming to arise from a mucosal base line rather

* References 7-10.

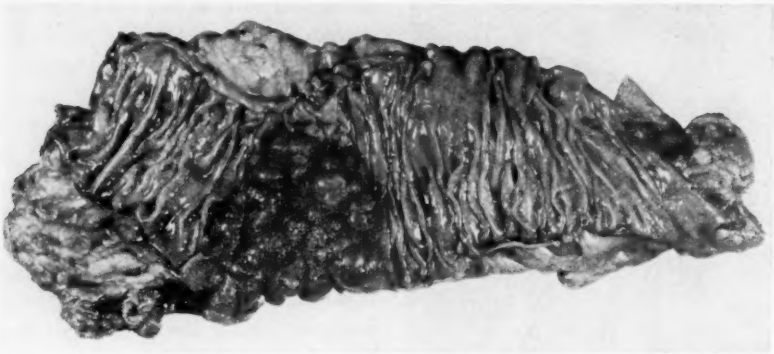

Fig. 2.—Villous polyp of the rectum.

than from a common stalk. Such papillary fronds are covered with a surface type of intestinal epithelium which is fairly well differentiated, although the cells are frequently more crowded than the normal and have more hyperchromatic nuclei. Few glands are formed within the typical villous polyp. Mucus secretion is quite variable; goblet cells are rather frequent. Inflammatory cells are not prominent either in the stromal fronds or at the base of the polyp. The junction with the adjacent normal mucosa is sharp and superficial and gives the impression that the tumor cells spread along the mucosal surface to replace adjacent normal cells; this is particularly suggested by the fact that normal mucosal glands are often present beneath superficial tumor cells (Figs. 3 and 4).

Not all the villous polyps are so typical. Not only are there many which show transitional forms to the usual adenomatous polyp, but some show so-called "atypism" or atypical hyperplasia. This is evidenced by the individual epithelial cells becoming irregular and pleomorphic, with increased hyperchromatism of nuclei and increased numbers of mitoses. In such instances, in addition, the epithelium becomes progressively piled up, as though it were growing too rapidly to remain within its usual bounds.

With progressive atypical changes, the suspicion of carcinoma likewise increases, but the diagnosis of carcinoma, made from atypical mucosal growth alone, is difficult and should be made with extreme caution.

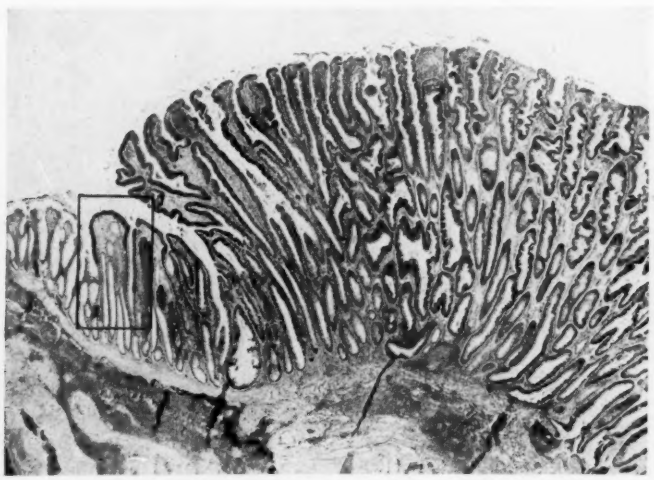

Fig. 3. — Typical villous polyp, benign, with the usual prominent villous fronds. Note abrupt transition, with normal mucosa on the left. Removal of this polyp by snare and cautery may not destroy the abnormal epithelium at the edge of such a tumor, thus accounting for later recurrence.

Fig. 4.—Higher magnification of specimen shown in Figure 3, demonstrating transition of "spreading" layer of cells over surface to a point of contact with normal mucosa. The underlying mucous glands are normal, emphasizing the surface epithelial peripheral spread of these tumors.

The only reliable criterion of carcinomatous change in a polyp is invasion of stroma or of vessels. It is true, however, that the polyps that are most likely to show such invasive changes are those that show atypical hyperplasia. The focus of carcinoma may be extremely small, and it is important to examine multiple sections of all polyps that show any evidence of atypicality in epithelial growth. Biopsy specimens (Fig. 5) are often difficult to examine and evaluate because of their fragmentation; this is due to lack of sufficient stroma to bind the epithelial fronds together. It is necessary to examine multiple sections to determine the exact amount of cancer that is present, since the pathologist is obligated to include in his report not only the presence of cancer but a rough estimation as to the extent of cancer in the polyp.

Comment.—Villous polyps appear to be but variants of adenomatous polyps, since it is possible to find cases that seem to represent transition forms between the two. The outstanding microscopic feature of the villous polyp is the accent of surface epithelial growth, with a progressive replacement of the adjacent epithelium, rather than a formation of numerous glands with relatively little change in the overlying epithelium, as is often seen in adenomatous polyps. Villous polyps are slow-growing, low-grade neoplasms. The diagnosis is best made from the clinical examination of the intact gross specimen. The diagnosis of villous polyp cannot be made consistently on a histologic basis, but the clinical impression may be confirmed. The main function of the microscopic exami-

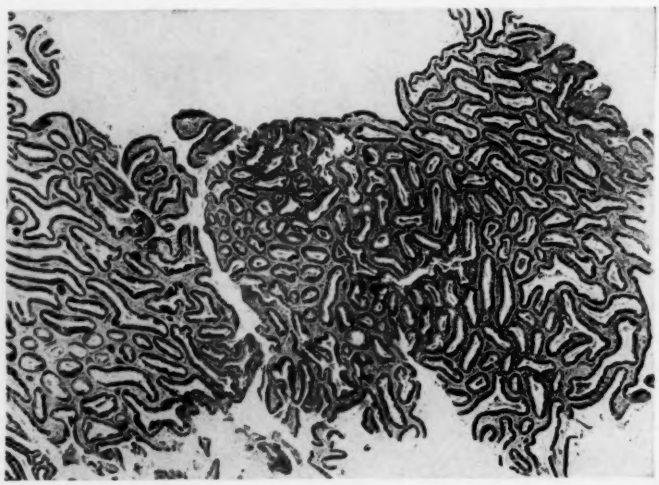

Fig. 5.—Microscopic appearance of typical biopsy specimen of villous polyp, showing the usual lack of stalk or significant stroma and the tendency toward fragmentation. Villous tumors usually cannot be distinguished histologically from adenomas in biopsy specimens.

nation is to look for carcinoma and to determine the extent of carcinoma if it is present.

CLINICAL DATA, TREATMENT, AND RESULTS

The average age of our 52 patients was 59 years. The oldest patient at the time of diagnosis was 74; the youngest, 36. Only four patients in this series were under 50 years of age; all were women, 36, 38, 40, and 43 years, respectively. There were 25 men and 27 women.

The symptomatology presented by these patients is shown in Table 2. In general, the symptoms resulting from these tumors are extremely variable and usually indistinguishable from those of cancer. The predominant

TABLE 2.—*Symptoms Due to Villous Polyps*

	Cases	
	Number	Per Cent
Rectal bleeding	38	71.7
Diarrhea (all types)	28	52.8
Mucous	11	20.7
Watery	8	15.0
Not stated	9	16.9
Alternating diarrhea and constipation	4	7.5
Constipation	3	5.6
Prolapse of rectum or tissue	6	11.3
Low abdominal pressure	3	5.6
Rectal pressure	1	1.8
Rectal pain	1	1.8
Passage of tissue	3	5.6
No symptoms	4	7.5

symptom is rectal bleeding associated with diarrhea. The diarrhea may be variously described as bloody, jellylike, watery brown, or mucous. It may vary from a simple passage of mucus through the rectum to a mucous or watery diarrhea of 12 to 15 stools a day. Alternating constipation and diarrhea was noted in four cases, and constipation alone, in three instances. Rectal pain is rare. Cramplike abdominal pain also is not a frequent symptom and, when present, is probably on a mechanical basis. Passage of bits of tissue from the rectum had been observed by three patients. This symptom probably occurs more frequently than this incidence would indicate, because many patients might not make this observation. Four patients of the group had no symptoms referable to their tumor.

The 35 patients reported in this study are analyzed in Table 1. The diagnosis, method of treatment, and status after five or more years of observation are listed. If more than one diagnosis was made as a result of repeated biopsies, the diagnosis given was based on the greatest degree of atypicality or malignancy seen in any of the specimens. For example, if a tumor was reported on several occasions as a benign mucosal polyp but on subsequent study either atypical hyperplasia or early carcinoma was found anywhere in the removed tissue, it was recorded as mucosal polyp with atypical hyperplasia or mucosal polyp with early carcinoma, as indicated.

Of the 35 patients observed for five or more years, adenocarcinoma developed in 5, or 14.3%, at some time during their course. In addition, small foci of early carcinoma developed in six cases, or 17.1%. Therefore, in 31.4% of this series some stage of cancer developed.

Of the 11 patients (31.4%) in whom carcinoma developed, 8 were submitted to abdominoperineal or a Miles type of resection (72.7%). Two of the remaining three were treated by snare excision and fulguration of the tumor and have been well without evidence of recurrence five and six years, respectively. The third patient was treated by local excision and has been well without evidence of recurrence for 10 years.

Of the seven patients (20%) with atypical hyperplasia, four were treated by snare excision and fulguration only. One of these has a benign recurrence at present; the other three are well without evidence of recurrence 6, 7, and 10 years, respectively. Two patients in this group had abdominoperineal resection, one because of excessive scarring and stricture formation and the other for a perforation at the time of fulguration. The seventh patient was treated by local excision of the tumor. These patients have been well 8, 10, and 13 years, respectively.

Of the 17 patients (48.6%) who had mucosal polyps, 11 were treated by repeated snare excision and fulguration only; 3, by

local excision; 2, by anterior resection, and 1, by abdominoperineal resection, this last case because of excessive scarring after 11 years of observation. Cancer did not develop in any of these patients during a period of continuous observation of 5 to 16 years.

There was no operative mortality in this series. Six deaths occurred after five or more years of observation from causes other than colon or rectal cancer.

COMMENT

This study has confirmed our clinical impression that villous tumors have a low-grade malignant potential, even though many develop localized areas of histologic cancer.

The incidence of histologic malignant change in our series during this period of five or more years was 31.4%. Sunderland and Binkley [3] reported 68%; Ewing,[2] 10% to 20%; Fisher and Castro [7] (in four cases) reported 100%, and Welch, McKittrick, and Behringer,[8] 22%.

It is interesting to note that Bacon [6] stated that in his 28 patients followed from two to seven years no deaths were attributable to the tumor per se. Binkley stated that in his 48 cases infiltrating carcinoma had not developed to date in any tumor that showed a uniformly benign structure originally and in the early recurrences. Gabriel stated that he has seen lymphatic spread from cancer superimposed on a villous tumor. In his series of seven patients who had been operated on five or more years previously, however, there had been no known deaths from metastases in a 19-year follow-up. In his series of 980 Miles resections done between 1932 and 1952 there were only 11 cases of villous tumor in which no malignant change could be found. In 98 cases in his series a malignant lesion was thought to have arisen on a preexisting benign tumor, which he believed was usually a villous tumor. He concluded, therefore, that cancer of the rectum arose as a result of malignant change in a benign tumor in approximately 10% of the cases (this corresponds to our previously reported figures [1]), and he believed that, because of this finding, more radical major surgery should be done for the large villous polyps, since malignant degeneration was so likely to occur. Our experiences do not differ materially from those cited; however, we cannot entirely agree with this conclusion.

Admittedly, the pathologic criteria for cancer in polyps which we have used are conservative. There must be the closest cooperation between the clinical surgeon and the pathologist. Decisions made for the diagnosis of cancer and for or against radical treatment in a given case must be the result of their joint study and experience. Our criteria for cancer and the indications for radical treatment have withstood for us the test of time. The decision of others should follow these same general principles. Diagnoses of cancer in villous polyps should certainly not be made without careful and, if necessary, repeated study of the complete tumor. The histologic study of our specimens varies with the size of the specimen, but ordinarily it involves a minimum of three different areas of each tumor, with multiple sections taken from each area. It is true, as has been stated,[7] that if serial sections of every entire villous polyp were made, the incidence of localized areas of malignant degeneration might be increased.

We are in entire agreement with Ewing as to the nature of the development of villous polyps. The principal change seems to be in the surface epithelium, and the polyps tend to spread laterally. We have long been impressed, however, with the high incidence not only of local but, in some cases, of apparently distant recurrences of these tumors. Not infrequently, a villous polyp low in the ampulla of the rectum has been eliminated completely and, somewhat to our surprise, it has recurred three to five years later at a much higher level, although still below the rectosigmoid area. This is probably the result of the incomplete removal or destruction originally of a very slow-growing type of tumor. If serial block studies were made in the future not only of the tumor area but of the entire removed segment of colon, we

would probably find that the area of epithelial change at the periphery of these tumors extends much farther than we have been aware of in the past. What other inherent growth defect there may be in this area of the colon which causes this growth variant of the mucosal polyp to develop, we do not know.

SUMMARY AND CONCLUSIONS

A series of 52 patients with papillary adenomas of the colon and rectum is presented. The age and sex incidence, symptomatology, location, and a brief description of the gross and microscopic pathological changes in these cases are given. In 35 patients the pathology, treatment, and end-results after five or more years are given.

Papillary adenomas of villous polyps usually occur singly in the rectum and recto-sigmoid areas of the colon in patients in the elderly age group. They are slow-growing and we believe have a low malignant potential, even though a high percentage will show atypical hyperplastic epithelial changes and many will even show early and localized histologic areas of cancer.

It is not our intention to advise or encourage needlessly any type of conservative treatment for cancer. We hold no brief for those who would sacrifice a person's future in a borderline case in an attempt to avoid an abdominal colostomy, should that be necessary. When adequate clinical and pathologic follow-up studies can be maintained, however, conservative approach seems justifiable for certain of these patients with villous polyps until the presence of actual cancer is proved.

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Diagnosis and Modern Treatment of Cerebral Vascular Disease

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As early as 1943, E. V. Allen and N. W. Barker [1] suggested that anticoagulants might be of value in the treatment of thrombosis of the cerebral arteries.

In 1946, one of us (I. S. W.) [2] reported experiences with anticoagulants in patients with cerebral emboli from myocardial infarction. In 1947, at the meeting of this same section of the A. M. A. convention,[4] we reported on cases of cerebral emboli from rheumatic hearts which were so treated. Four years later, in 1950,[3] a small series of cases was described in *Medical Clinics of North America*. Since then, many more patients have been treated and reported in the medical literature.*

Before the advent of successful therapy, either medical or surgical, the exact diagnosis of cerebral vascular lesions was purely academic. However, in the past two decades, surgery has shown great advances. Hematomas, both epidural and subdural, are now frequently relieved by surgery. Aneurysms which leak and produce subarachnoid hemorrhage can occasionally be resected.† The lesions of the brain which are not amenable to surgery, however, have been greatly neglected, although this constitutes one of the greatest problems in all of medicine. It has been estimated that there are some 2,000,000 Americans alive today suffering from cerebral vascular diseases. The neglect in this field of medicine is probably the result of the failure of any therapy to offer relief or prevention.

The three most important types of vascular lesions are cerebral thrombosis, cerebral embolus, and cerebral hemorrhage. It is most important to distinguish between these, especially if anticoagulant therapy is to be considered. The use of these drugs in the presence of cerebral hemorrhage is certainly unwarranted. In the majority of instances the differential diagnosis is relatively easily made. Usually the clinical history, physical examination, and laboratory studies make the differentiation between the three major types. However, there are borderline cases in which all factors must be considered. To aid in this differential diagnosis, we have composed the accompanying Table, which summarizes the major points of differential diagnosis.

In the diagnosis of acute episodes of cerebral vascular disease, a lumbar puncture properly done is an essential procedure. If there is evidence of increased intracranial pressure, as indicated by papilledema, it is recommended that not more than 0.5 ml. of fluid be removed, drop by drop. This amount will be sufficient for the essential laboratory examination. A recent study of 108 consecutive cases of brain tumor made by Erman ‡ has demonstrated that the dangers associated with this procedure have been exaggerated. This confirms our experience.

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* References 4-9.

† Bucy, P. C.: Neurosurgical Aspects and Therapeutic Approach to Cerebral Vascular Disease, in Wright and Luckey.[10]

‡ Erman, S. L.: A Consideration of Lumbar Puncture in the Diagnosis of Brain Tumor: A Review of 108 cases, unpublished data.

Differential Diagnosis of Intracerebral Hemorrhage, Cerebral Thrombosis and Cerebral Embolus

	Cerebral Hemorrhage	Cerebral Thrombosis	Cerebral Embolus
Onset	Severe headache, nausea and vomiting frequently occur at onset, followed by coma	Difficulty in speaking and weakness of arm or leg are the usual first symptoms; onset may be gradual or sudden	Very sudden, abrupt development of neurological signs
Convulsions	Convulsions occur in 14% of patients at onset	Convulsions occur in 7% of patients at onset	Convulsions may occur
Coma	If coma persists more than 24 hours, hemorrhage more likely	Coma usually less than 24 hours; often none at all	Coma not usual unless embolus is large
Incidence	15%	82%	3% *
Age groups	Same as for arteriosclerosis (increasing with each decade over 50)	Same as for hemorrhage	As majority of cases occur from rheumatic hearts, most patients are young adults or early middle-aged
General physical examination	Evidence of arteriosclerosis in retinal or peripheral vessels or other evidence of disease of cardiovascular system; blood pressure often elevated; Stevenson states that on his autopsied patients the systolic pressure has almost always been above 200 mm. Hg	Same as for hemorrhage	Rheumatic heart disease with mitral stenosis; bacterial endocarditis; auricular fibrillation from any type of heart disease; recent myocardial infarction; evidence of emboli elsewhere such as in the lungs, arms, legs, kidneys, or mesentery may be present; usually at least one of these pathological states can be found
Cheyne-Stokes or labored respiration	Common	Seldom	Rare
Conjugate deviation of eyes	Frequent	Seldom	Rare
Quadriplegia	Rare	Rare except in thrombosis of basilar artery	Rare
Stiff neck	Frequent	Rare	Rare
Bilateral extensor plantar response (positive Babinski)	Frequent	Rare	Rare
Leucocytosis	More than 50% of patients have over 12,000 leucocytes per cu. mm.; counts greater than 20,000 are common	Uncommon	Uncommon unless embolus is infected
Cerebrospinal fluid			
Color	Usually bloody fluid is diagnostic of hemorrhage into either the ventricular or subarachnoid space; xanthochromic if hemorrhage is old	Usually clear	May be clear or slightly xanthochromic
Pressure	Increased	Normal to slightly increased; usually not above 250 cm. H_2O	Normal
Cells	Red cells may be crenated	Slight pleocytosis	Normal to moderate pleocytosis
Protein	Elevated	Normal to slight elevation	Normal to slight elevation
Mortality	90%	60%	50%

* While this figure is commonly accepted, the recent reports of Adams indicate it may be as high as 30%.

The electroencephalograph is sometimes useful in diagnosing cerebral vascular lesions. It is not, however, to be regarded as an infallible diagnostic procedure in differential diagnosis. Angiography has frequently proved helpful in the diagnosis and location of aneurysms and of some types of tumors, but it is of little or no value in the study of hemorrhage, thrombosis, or embolism and is not without appreciable risk.

CEREBRAL HEMORRHAGE

The location of the hemorrhage is of the utmost importance. Today surgery should be seriously considered for the relief of pressure of subdural or extradural hemorrhages. Patients frequently regain power and even consciousness promptly upon the removal of such pools of blood or clots. These hemorrhages most frequently occur following severe

trauma to the head, and this history is helpful in establishment of the diagnosis. Surgery should be performed promptly, preferably with the blood pressure markedly reduced. The commoner spontaneous cerebral hemorrhage does not as yet lend itself to specific therapy. Massive hemorrhage within or without the brain tissue frequently results in death, but autopsy studies suggest that many small hemorrhages may occur without death to the patient, in fact, in some instances without his knowledge of serious trouble.

FREQUENCY OF CEREBRAL EMBOLI

At the Conference on Cerebral Vascular Disease, held in Princeton, N. J., in January, 1954, Adams § pointed out that emboli are probably far commoner than had previously been suspected. Confirmation of this point of view now comes from an extensive study of autopsies by Towbin.[11] In a series of 525 consecutive autopsies performed at a large neuropsychiatric institution he found that 4% of all cases of organic brain disease were associated with recurrent cerebral embolism. The origin of these cerebral emboli is usually from the left side of the heart. Most frequently they arise from mural thrombi subsequent to myocardial infarction, secondly from thrombi within the left atrium associated with auricular fibrillation, due either to rheumatic heart disease or to arteriosclerotic disease. In an older study, Garvin [12] found that, in 6285 consecutive unselected autopsies, mural thrombi were present in the heart in 4.2% of all cases. Furthermore, he found that in 771 consecutive autopsies on adults who died of heart disease, intracardiac thrombi were present in 34.4%.

FREQUENCY OF CEREBRAL THROMBOSIS

The reported statistical incidence of cerebral thrombosis varies in different series. It is generally agreed that thrombosis is the leading cause of cerebral vascular accidents, the incidence reported being between 70% and 85%.

While it is not our intention to discuss various syndromes associated with occlusion of vessels in separate areas of the brain, it is of interest that occlusion of the internal carotid artery is a frequently unrecognized cause of cerebral vascular disease. Hunt [13] in 1914 summarized the older literature regarding this syndrome. Recently, Fisher [14] and Ochs and others [15] have reemphasized the necessity for examination of the common and internal carotid arteries for evidence of occlusion not only in the presence of hemiplegia and ophthalmoplegia but also in instances of senile dementia. Dunning [16] has described a simple but effective method of pharyngeal palpation of the internal carotid artery, and we strongly suggest that this examination be incorporated as a part of each physical examination in the presence of cerebral vascular disease.

TREATMENT OF THROMBOSIS AND EMBOLISM

In many hospitals the conventional form of therapy for cerebral thrombosis and embolism is still largely expectant. The patient is placed at rest and the so-called vasodilator drugs are used. The evidence that they increase blood flow to the brain or aid the situation in any way is decidedly inconclusive. When sedation is essential, chloral hydrate or paraldehyde are useful. In general, barbiturates are to be avoided.

The work of Kety ‖ and others demonstrated that increased CO_2 in the blood does increase the blood flow to the brain. The inhalation of this would therefore appear to be a sound therapeutic approach. We do not know for certain, however, that the mere passage of more blood through the vascular tree is necessarily beneficial if that blood is laden with increased amounts of CO_2. The use of stellate ganglion block has been advocated during recent years.[17] Favorable reports suggest striking improvement during the early days following a cerebral throm-

§ Adams, R.: Pathology of Cerebral Vascular Diseases, in Wright and Luckey.[10]

‖ Kety, S. S.: Physiology of the Cerebral Circulation, in Wright and Luckey.[10]

bosis. It is essential to bear in mind the natural course of this syndrome and the fact that many, if not most, of those patients show striking improvement during the first week or 10 days. Some patients have shown remarkable improvement coincident with the block, only to relapse shortly thereafter. It is very difficult to evaluate this procedure. Final evaluation of the indications and usefulness of it must await more extensive experience.[18] At present the trend appears to be against its general acceptance.

The use of anticoagulant drugs in cerebral embolism or thrombosis is based on the following objectives: first, to prevent new emboli from forming in the heart or aorta; second, to prevent propagation of the original thrombus, which might occlude additional branches of the involved artery, thus increasing the size of the infarcted area; third, to prevent the development of additional thrombi in other vessels, a common occurrence in the brain, and, fourth, to encourage the more rapid disintegration of the original thrombus by the enzyme systems in the blood, which may have a freer action in the presence of adequate anticoagulant therapy.

There is an additional valid reason for giving anticoagulant drugs to these patients. Most of them are severely ill and confined to bed. Many have an increased tendency to thrombosis. Phlebitis, pulmonary embolism, and other thromboembolic episodes are common. In the Cornell Second Medical Division of Bellevue Hospital ¶ during a 10-year period, from 1942 to 1952, ninety-eight patients with cerebral vascular diseases were autopsied. More than half these had major thrombi elsewhere in addition to their cerebral disease; 46 of these 98 cases were patients with cerebral thrombosis or embolism, and 52 of the 98 cases were patients with cerebral hemorrhage. Even in this group of cerebral hemorrhage cases, a great many had thromboembolic complications; actually, 17 patients had 23 such complications. Since our early reports on the use of anticoagulant drugs there have been other reports in the medical literature.# In a recent study by Millikan, Siekert, and Shick, of the Mayo Clinic,[21] a group of patients with thrombosis of the basilar artery were so treated. Favorable results were obtained. Perhaps Dr. Siekert will have something to say about this in his discussion of this subject.

Today, we would like to present to you the findings of 57 patients with various types of cerebral thromboembolic episodes whom we have treated with anticoagulants. Of this total of 57 cases 31 are patients with rheumatic heart disease and 19 are patients with cerebral thrombosis or embolism on the basis of arteriosclerosis. The remaining seven cases consist of miscellaneous diseases.

The most impressive results have been obtained in the patients with rheumatic heart disease. In a period of 464 months, 31 patients who were under observation developed 137 major episodes of thromboembolism and of these there were 46 cerebral vascular episodes. During the next 710 months, in which time they received anticoagulant therapy, there were only 11 thromboembolic episodes, of which 4 were cerebral vascular. Illustrative case histories follow.

PATIENT 3.—A 53-year-old white woman with rheumatic heart disease developed auricular fibrillation and one year later had a transient period of left hemiparesis. Two years later she had a myocardial infarct, and two months later, an embolus to the right popliteal artery. Anticoagulants were begun at this time and continued for 42 months without further embolic episodes until it became necessary, it was thought, to reduce her anticoagulant level to allow for the extraction of a tooth. There was an unforeseen delay in extraction, and the patient remained off anticoagulants for nine days. Anticoagulants were started again the day of extraction, but before there was a sufficient protection, and at a prothrombin time of 18.2 seconds, she had a transient left hemiparesis and also an embolus to the right brachial artery. These both cleared rapidly. Anticoagulants were continued, and she remained in her usual state, able to do light housework and make weekly visits to

¶ McDevitt, E.: Anticoagulants and Their Place in the Treatment of Cerebral Vascular Diseases, in Wright and Luckey.[10]

References 19 and 20.

the anticoagulant clinic, until Sept. 9, 1953, almost six years to the day of her being placed on anticoagulants, when she was admitted to another hospital service with evidence of left cerebral damage. The prothrombin time on admission was 19.4 seconds. The patient remained in comatose state during the 10 days of hospitalization. She received Depo-solution heparin; however, no clotting times were reported. The prothrombin time did not exceed 23 seconds. At autopsy there was evidence of two anemic infarcts on the right, and in the left internal capsule there was a large hemorrhagic infarct. Whether the final episode was hemorrhagic or embolic is difficult to say. It is conceivable that embolization occurred and that with the prolongation of clotting time by heparin excessive bleeding ensued.

PATIENT 4.—A 41-year-old white male artist was admitted to New York Hospital for evaluation before valvulotomy. He had previously experienced four arterial emboli and had been maintained on anticoagulants for a period of 14 months without embolization. Anticoagulants were discontinued one month and three days prior to the operation, a period we now consider too long. At the time of operation a thrombus was found in the auricular appendage, which was not flushed out, as is now done routinely. When the patient recovered from the anesthesia it was found that he had a right hemiparesis. He was immediately restarted on anticoagulants and has had no further embolization in the subsequent 43 months.

This patient illustrates a complication of cardiac surgery which can be crippling or fatal. McGoon and Henly [22] report that 13.5% of patients whose hearts were in fibrillation prior to commissurotomy developed cerebral emboli during the period of anesthesia. In the presence of normal sinus rhythm only 2.8% of their series experienced the same complication. In the past two years we have seen 14 patients who have developed thromboembolic complications at the time of cardiac surgery either during the period of anesthesia, the immediate postoperative period, or subsequently. Of these 14 thromboembolic complications 5 were cerebral.

The technique of intermittent common carotid and left innominate artery occlusion suggested by Bolton and others [23] has not been a satisfactory method of prevention of this complication.[24]

It has been suggested [25] that after a patient has survived the operative period without embolization there is no further danger of this complication. This had not been our experience nor that of others.[24] We therefore suggest that in the preparation of patients for valvoplasty anticoagulants be used for a period of approximately six weeks prior to surgery in order to allow any thrombi present in the atria to be sealed over and thus prevent embolization from fibrillating extensions of the thrombi. At the time of surgery, anticoagulants should be withdrawn, and they should be restarted three to four days thereafter. This technique is of especial importance in those patients whose hearts are in fibrillation or who have suffered from previous emboli.

ARTERIOSCLEROTIC DISEASE

Nineteen patients were treated who suffered cerebral vascular accidents which were on the basis of embolization from a mural thrombus secondary to myocardial infarction or to thrombosis of a cerebral artery. Eight of these patients suffered 13 myocardial infarctions preceding other thromboembolic episodes. Thirteen of the nineteen patients were hypertensive. In 248 months, during which time they were observed and treated before anticoagulant therapy was started, there were 48 major thromboembolic episodes, 25 of which were cerebral. During the period of anticoagulant therapy, namely, 287 patient-months, the same patients suffered only 8 thromboembolic episodes, of which 2 were cerebral. A typical case history follows:

PATIENT 9.—A 53-year-old white man at the age of 50 experienced his first myocardial infarction, which was mixed in type. He was admitted to New York Hospital, and anticoagulants were begun on July 20, 1950, effective levels being reached within 72 hours, although they dropped below therapeutic levels on six occasions. The patient made a satisfactory recovery and was discharged after 30 days. Anticoagulants were discontinued at that time. Seven months later the patient suddenly developed pain and coldness in the left lower extremity from the knee down; anticoagulants were not given. Eleven months after this episode he developed evidence of a left hemiparesis, which was transient, the only residual being a left facial weakness. Eight months later the second myocardial infarction occurred in the

posterior base, and the patient was again placed on anticoagulants, this time for 40 days. On discharge, anticoagulants were again discontinued, and three months later he developed sudden coldness and pain in the entire right lower extremity; an embolus was removed from the right femoral artery and anticoagulants were reinstituted. The patient remained under this therapy for the next 19 months, at which time he died suddenly of a cardiac arrhythmia. During his anticoagulant therapy he was free of thromboembolism.

The other seven patients in this series have a variety of vascular condition, including migratory phlebitis, migratory phlebitis with Cooley's anemia, congenital heart disease, polycythemia vera, auricular fibrillation, and pseudobulbar palsy.

During a period of 83 patient-months there were 20 thromboembolic episodes, 10 of which were cerebral. In 165 months on anticoagulant therapy there were four episodes, none of which was cerebral, and none of which occurred at adequate prothrombin levels.

HEMORRHAGE

A total of 29 hemorrhagic complications occurred in nine patients during anticoagulant therapy, most of them minor in nature.

COMMENT

No discussion of the treatment of cerebral vascular disease would be complete without mention of the role of physical medicine. As soon as the condition of the patient has become stabilized, an evaluation of the degree of impairment should be made and a comprehensive plan for rehabilitation proposed. This should include physical, emotional, and occupational guidance and should be begun early so that contractures, decubiti, atrophy of muscles, and mental and emotional depression can be avoided.

The problem of the diagnosis and treatment of cerebral vascular disease requires the combined efforts of the physician, surgeon, neurologist, and physiatrist.

Value of Anticoagulants in the Treatment of Cerebral Accidents.—It is difficult or impossible to obtain conclusive evidence which indicates that the use of coagulants has influenced the immediate course of a particular patient after a cerebral vascular accident has occurred. It is, however, the impression of numerous observers that a favorable influence has been exerted. To accumulate additional evidence regarding this point a comparable group of control and treated patients must be studied; such a study is now in progress.

SUMMARY

Cerebral vascular diseases are among the most serious and commonest diseases.

The present state of knowledge of these diseases and the present results of treatment are far from satisfactory.

Differential diagnosis is no longer of purely academic interest, and various methods to aid in diagnosis are discussed.

Vasospasm occurs in the cerebral aretries and is of importance in terms of warning of more serious phenomena to come and also because treatment may be of some help in preventing the serious consequences.

Cerebral hemorrhage is always serious. Surgical methods may be seriously considered for subdural or extradural hemorrhages. Most other cerebral hemorrhages are not amenable to specific therapy at this time.

The use of sympathetic blocks for acute thromboses or emboli is under study at present; final evalution remains for the future.

The use of anticoagulant drugs for the treatment of thrombosis and embolism during the acute stage is in the process of investigation. Their trial appears justified, but future experience is essential for final evaluation.

Experience with the use of anticoagulants in the reduction of recurrent thromboembolic episodes in 57 patients treated for a total period of 1162 months is summarized.

Fifty-seven patients during a period of 795 patient-months before beginning anticoagulant therapy experienced 205 thromboembolic episodes, 81 of which were cerebral in location. Following institution of anticoagulant therapy, during a period of 1162 patient-months, these patients experienced 23 thromboembolic episodes, 6 of which were cerebral in location.

A reduction in incidence appears to have occurred in emboli arising from thrombi in the hearts of patients suffering from rheumatic heart disease or from acute myocardial infarction.

A reduction in the incidence of recurrent thromboses in the arteries of the brain has been noted.

There has also been a reduction in the number of venous and arterial thromboses occurring elsewhere in the body.

The risk from hemorrhage in the treatment of these diseases with anticoagulants is present but not excessive.

ABSTRACT OF DISCUSSION

DR. ROBERT G. SIEKERT, Rochester, Minn.: It is a pleasure to comment on Dr. Foley's excellent paper. He and his associates have done us a great service by discussing the diagnosis and treatment of cerebrovascular disease. Particularly is this true in regard to their method of therapy for the recurrent cerebral emboli which occur as a consequence of rheumatic heart disease. The data presented certainly indicate the great value of such therapy. Here they have extended their fine work on the treatment of certain cardiovascular diseases to the treatment of certain cerebrovascular diseases. In recent years more attention has been given to this cardiocerebral axis, and the interrelationships have been more clearly appreciated. Not only arteriosclerosis, myocardial infarction, and embolic phenomena but altered dynamics of the general circulation from any cause are important in the production of cerebral infarction. Additionally, the concept of prevention of cerebral damage by treatment before such damage can come about deserves, I believe, very special emphasis.

Strokes occurring subsequent to myocardial infarction may cause some difficulty in diagnosis. The catastrophic appearance of neurologic abnormalities certainly suggests embolism; yet embolism is not always the causative factor, even with this type of onset. Evidence of extracerebral emboli may be an important diagnostic factor. In either event—whether cerebral embolism or thrombosis is present—the routine use of anticoagulant therapy in myocardial infarction suggests itself for use, at least, in the prevention of cerebral complications. Here again, one wonders if such treatment can be instituted immediately after the ictus, and I wish Dr. Foley would comment on this aspect of treatment, that is, can one safely begin anticoagulant treatment immediately after the occurrence of cerebral embolization?

Like the authors, I have been concerned also with prevention of cerebral damage by advance treatment. My own work has been concerned principally with three groups of patients. Two of these concern states of intermittent insufficiency, involving, respectively, the basilar and the carotid arterial systems. The other is thrombosis within the basilar system. The laminated appearance of a thrombus in the basilar artery and the frequent step-wise progression of neurologic abnormalities when this artery becomes occluded suggested the usefulness of anticoagulant therapy. The transient episodes, so very common in patients who subsequently sustain thrombosis of the basilar, were then looked upon as precursors to actual occlusion. This observation also appears to be true in carotid thrombosis. Thus, in the instances of episodic insufficiency, prevention of any damage, and in the "thrombotic" syndrome prevention of more damage, have been the goals in therapy.

To date, the results obtained for patients whose condition was limited sharply to these categories have been extremely encouraging. The intermittent episodes have ceased. For instance, a 55-year-old woman who had many transient episodes of blindness in the left eye and contralateral hemiparesis and numbness, increasing in frequency and severity, gained relief when she received anticoagulant therapy. In the others, the thrombotic process, presumed to be advancing, has been checked, provided treatment was instituted early. In many patients of this last group, a surprising return of function has been observed. Cortical blindness, partial third-nerve palsy, and bilateral corticospinal-tract dysfunction developed successively, over three days, in a 54-year-old man; after a month of treatment he had only a minimal scotoma.

The limits of this form of therapy have not yet been determined. One wonders about its use in recurrent focal infarctions or after a single stroke to prevent any more. For the present, caution need be exercised in its use, since obvious contraindications are present. The material presented today by Dr. Foley and by me suggests that effective treatment is available in a significant number of patients with cerebrovascular disease.

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Case Reports

XANTHOMA DIABETICORUM

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XANTHOMA diabeticorum is a rare complication of diabetes mellitus which dramatically calls attention to the derangement of fat metabolism which occurs in diabetes and to the effectiveness of diabetic control in correcting this defect.

Xanthoma diabeticorum was first described by Addison and Gull, in 1851.[1] In the preinsulin era this condition was commoner than it is today. Related publications in recent years have been few, and xanthoma diabeticorum is considered to be a rare complication. Only 14 of Joslin's * 21,000 cases of diabetes mellitus had this complication. In Thannhauser's classification of the xanthomatoses,† it falls into the group of secondary xanthomatoses due to hyperlipemia. In contrast to the primary essential xanthomatoses, which are constitutional disorders of the intracellular metabolism of reticuloendothelial cells, the secondary types are manifestations of hyperlipemic states. With correction of the increased blood lipids, reabsorption of the deposited lipids occurs and the eruptive lesions disappear.

Characteristically, the diabetic state is associated with a distorted fat metabolism with frequent occurrence of lipemia and hypercholesterolemia. In diabetic lipemia the neutral fat fraction is increased most, while the cholesterol and phospholipid fractions are increased less or not at all. Hirsch and coworkers [4] have shown that hyperglycemia is associated with a hyperlipemia, the intensity of which seems to approximate the severity of the hyperglycemia. With correction of the hyperglycemia, the esterfied fatty acids of the blood return to a high-normal range. They also have shown that the blood lipids during a fat-tolerance test are much higher when the diabetic patient has hyperglycemia than when he is normoglycemic.

A clinical and laboratory study of 18 patients admitted in diabetic acidosis was done by Tuller and co-workers.[5] Although no precise correlation could be observed between blood sugar and CO_2 values and either cholesterol or lipoprotein values, a general relationship between the serum lipid deviation and the degree of acidosis was observed. Successful therapy was followed by a rising serum CO_2 and by a fall in serum lipoproteins and cholesterol levels. Treatment, however, did not result in a return of the lipids to a normal level for persons of the same age and sex. The authors further stated that they have seen no patient in diabetic acidosis without some increase in the serum lipoproteins. It has also been noted that serum lipids are more increased in diabetic patients with vascular changes than in those with no such complications.

In xanthoma diabeticorum there is an exaggeration of the usual lipid disturbance seen in the diabetic patient. A deficiency of insulin, either absolute or relative, is responsible for a reduced carbohydrate utilization in the diabetic state. Fat catabolism provides the fuel requirement of the body, and the resultant lipemia reflects the increase in transportation of lipid substances from fat depots to the liver. At the latter site, the lipid substances are transformed into ketone bodies which are then metabolized for energy production.

In xanthoma diabeticorum the neutral fat is usually increased to a degree where the

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* Reference 2, pp. 593-595.

† Reference 3, pp. 201-208.

serum is of a milky appearance. However, this need not be so, for neutral fats may be increased by 150% ‡ without the appearance of a lactescent serum. Boyd [6] states that the extent of milky appearance of the serum is related to the proportion of different lipids in the blood serum. Phospholipids are hydrophilic, and the lower their concentration in the serum proportional to other lipids the more likely will the serum be milky. The phospholipids act as emulsifiers and permit colloidal solution of greater amounts of other lipids.

The basic lesion of xanthoma diabeticorum consists of nests of foam cells surrounded by connective tissue and inflammatory reaction. The foam cells are histiocytes which have phagocytized the serum lipids. Chemical analysis of the xanthomatous lesions shows an excess of fatty substances other than cholesterol. It was noted by Wile and co-workers [7] that cholesterol occurs to the extent of 16% of the lipids present and comprises only 2% of the solid content of the lesion.

The skin lesions are multiple small yellowish nodules, often surrounded by inflammatory halos. They vary in size, some having a diameter as great as 5 mm. They appear suddenly, spread rapidly, and have a predilection for the gluteal area and the extensor surfaces of the elbows and knees. Any organ which contains reticuloendothelial cells may show a similar involvement. Phagocytosis of lipids may occur in the spleen, and at autopsy the spleen may be enlarged, with scattered nests of foam cells. An enlarged liver is a frequent finding, and fatty infiltration is the prevailing pathological change. Characteristically, liver-function tests reveal no impaired function. Montgomery and Osterberg [8] reported lipemia retinalis in four of their nine cases of xanthoma diabeticorum. Four of Joslin's § twelve cases had lipemia retinalis. Thannhauser || states that diabetic patients suffering from hyperlipemia and hypercholesteremia are early doomed to become subject to atheromatosis and arteriosclerosis.

‡ Reference 3, p. 28.
§ Reference 2, p. 495.
|| Reference 3, p. 206.

REPORT OF CASE

J. L., a 31-year-old white man, entered the hospital on Oct. 31, 1954. Four months prior to admission he noted the insidious onset of polydipsia and polyuria. In spite of a good appetite a 15 lb. weight loss occurred. One month prior to hospitalization, discrete asymptomatic papular lesions appeared on both elbows. They increased in number and size and were followed by the appearance of similar lesions on the knees, forearms, and gluteal regions.

The patient's family history was negative for diabetes mellitus, xanthomatous diseases, and premature arteriosclerotic vascular complications. Several urinalyses obtained during an unrelated admission three years previously failed to show glycosuria.

Physical examination revealed a well-developed well-nourished white man of 135 lb. and 65 in. Temperature, pulse, and respirations were normal. Blood pressure was 130/50 mm. Hg. No scleral icterus, xanthelasma, or arcus was seen. Funduscopic examination showed no arteriosclerotic changes or evidence of change in color of the retinal vessels. The ears, nose, and throat were normal. No evidence of dehydration or infection was present. The neck was supple, and the thyroid was not palpable. The heart and lungs were normal. The abdomen was soft, and there was no tenderness to deep palpation. The liver extended 4 cm. below the right costal margin; it was smooth and nontender. No other abdominal mass or organ could be palpated. The genitalia and rectum were normal. Peripheral arterial pulsations were palpable. There was no palpable lymphadenopathy. Neurological examination showed normal deep tendon reflexes and no sensory or proprioceptive disturbance.

Numerous discrete yellowish nodules were seen scattered over the gluteal area (Fig. 1) and the extensor surfaces of the elbows and knees (Fig. 2). They varied in size from 1 to 3 mm. in diameter, and many were surrounded by inflammatory halos. They were hard and nontender. The intervening skin was normal.

Admission hemoglobin was 15 gm. per 100 cc.; white blood cell count, 72 per cubic millimeter, with a normal differential count. The sedimentation rate (Wintrobe) was 33 mm. in one hour. Admission urinalysis revealed 4+ sugar and 2+ acetone; protein and microscopic study were negative. The fasting blood sugar on admission was 315 mg. per 100 cc.; the CO_2 was 20 mEq. per liter, and the nonprotein nitrogen was 32 mg. per 100 cc. Phenolsulfonphthalein excretion was normal. Sulfobromophthalein (Bromsulphalein), prothrombin time, cephalin flocculation, thymol turbidity, and alkaline phosphatase studies were normal.

The blood serum was lipemic (Fig. 3). Total cholesterol was 740 mg. per 100 cc., and a total

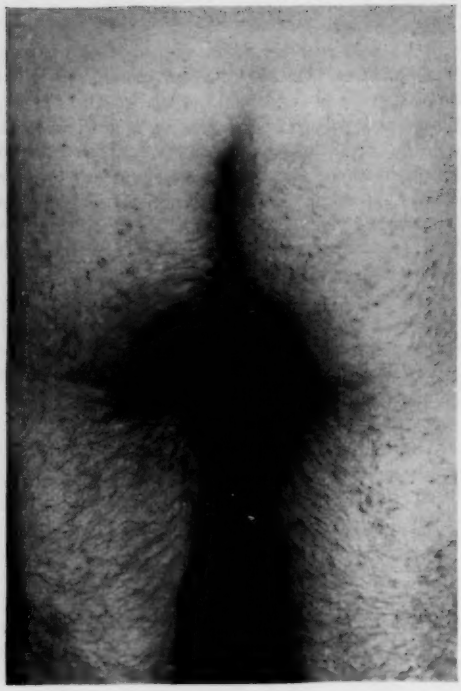


Figure 1

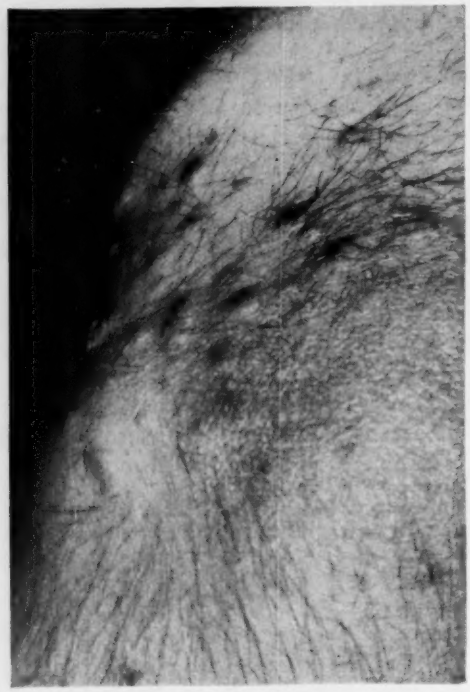


Figure 2

Figure 3

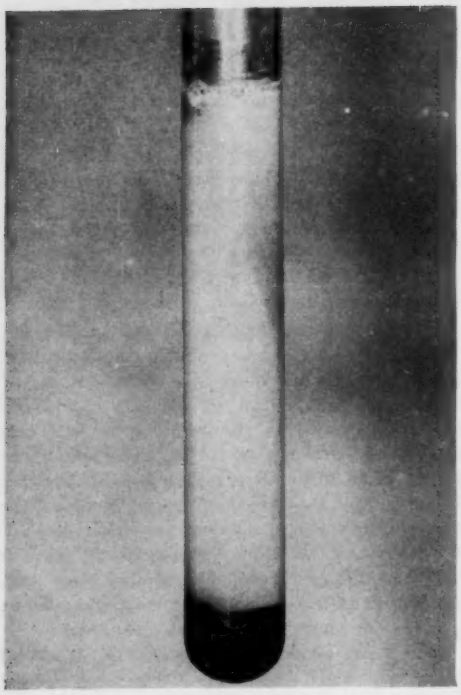
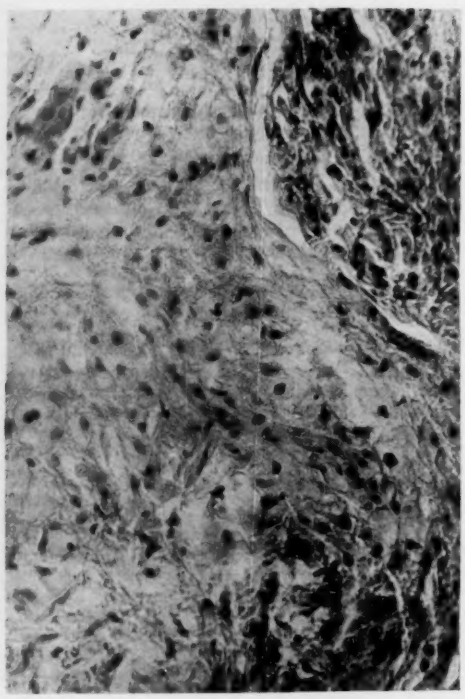


Figure 4

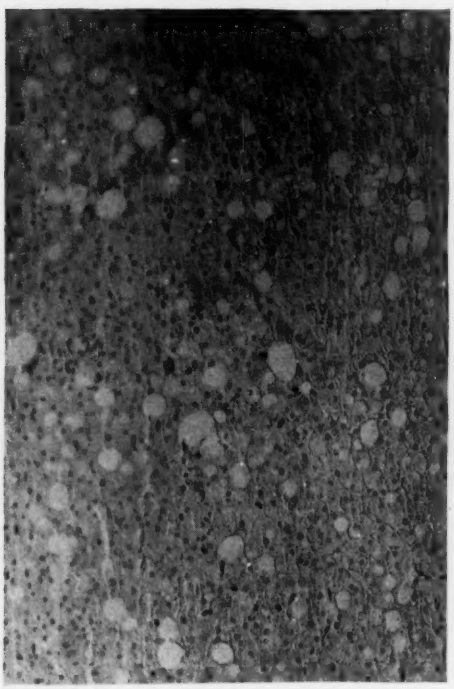


lipid determination one week after therapy was begun showed a level of 2970 mg. per 100 cc. (normal total serum lipids according to Peters and Van Slyke, 570 to 820 mg.). The chest film and electrocardiogram were normal.

On admission the patient was placed on an 1800 Cal. diet consisting of 180 gm. carbohydrate, 80 gm. protein, and 80 gm. fat. Initially regular insulin was given according to the glycosuria in the fractional urines, and the maximum amount received in one 24-hour period was 30 units. One week later the patient was placed on 20 units of isophane insulin (NPH insulin) daily. Within 72 hours of hospitalization the urine was free of acetone. By the second week glycosuria had been corrected; the blood sugar was within a normal range; the serum was no longer lipemic, and the xanthomatous lesions had begun to regress. At that time the total cholesterol had dropped from the admission level of 740 mg. per 100 cc. to 285 mg.

A biospy of a skin lesion taken during the first week of hospitalization showed foam cells surrounded by an area of inflammation (Fig 4). A liver biopsy at the same time showed fatty metamorphosis of the liver (Fig. 5). Seven weeks after admission the xanthomatous skin lesions had completely cleared from the arms and knees and disappearance of the lesions in the gluteal areas was nearly complete. At that time a repeat liver biopsy

Figure 5



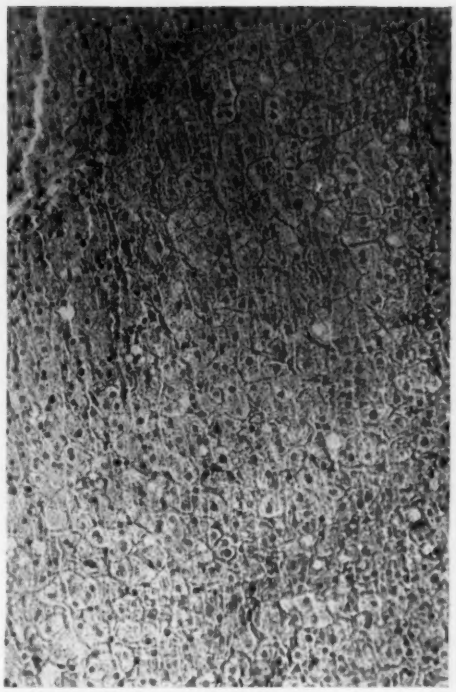


Figure 6

(Fig. 6) showed considerable reduction in the degree of fatty metamorphosis.

Two weeks after beginning therapy the patient began to experience the first of several forenoon insulin reactions. Insulin was gradually reduced. Because of freedom from glycosuria and low fasting and two-hour postprandial blood sugar levels while he was given only 12 units of isophane insulin, the decision was made to attempt to control the diabetes mellitus by diet alone. Dietary control of the diabetes without insulin proved successful.

COMMENT

This patient's dramatic response to therapy confirmed the diagnosis of xanthoma diabeticorum. The differential diagnosis of xanthoma must include several other conditions.

The lesions of xanthoma tuberosum, although of a similar distribution, appear insidiously, are fewer in number, and are larger in size. Grossly and microscopically they show less of an inflammatory appearance. They are a primary essential xanthoma of hypercholesteremic type, and the elevated serum cholesterol occurs without hyper-

lipemia. The serum therefore does not appear lactescent. The lesions of xanthoma disseminatum are, as implied by the name, widely disseminated, and any organ of the body may be involved. Diabetes insipidus and exophthalmos are occasional findings. The lesions of xanthoma disseminatum have a predisposition for the flexor surfaces of the extremities, the face, and the axillae. They are a primary xanthoma of a normocholesteremic type with no associated increase in neutral fat.

Patients subject to idiopathic hyperlipemia appear healthy, while the patient with xanthoma diabeticorum appears ill. The xanthoma of idiopathic hyperlipemia and the hyperlipemia tend to disappear with marked restriction of dietary fat. Such a diet does not benefit the patient with xanthoma diabeticorum. When the patient with idiopathic hyperlipemia has an associated diabetes, and insulin is given, the diabetic state is corrected but the hyperlipemia persists.

Fat restriction has been advised ¶ in the therapy of xanthoma diabeticorum, in addition to adequate doses of insulin. Daily fat allotments have varied from a conservative reduction to a starvation level of 20 gm. The necessity for this reduction is questionable, since there is no direct relation between ingested fat and the exaggerated hyperlipemia seen in this complication of diabetes. Insulin will correct the hyperlipemia by restoring the ability of the liver to utilize carbohydrate. As demonstrated in our case, adequate treatment of xanthoma diabeticorum by means of insulin and a diet low in carbohydrate and calories with no reduction in fat was adequate to produce a prompt disappearance of the hyperlipemia, the fatty liver, and the xanthomatous eruption.

The fact that our patient's diabetes mellitus was eventually well controlled on diet with no insulin was unexpected. It supports the statement by H. C. Shepardson # that "the severity of diabetes, as measured by the insulin dosage is far less important as a cause of disturbed lipid metabolism than is the degree of control of the diabetes."

¶ References 9-12 and Reference 2, pp. 593-595.

In discussion on Tuller.[5]

SUMMARY

A case of xanthoma diabeticorum is described, including the findings in biopsies of the skin and liver. The response of both the skin lesions and the fatty liver to ordinary measures of diabetic control, with no reduction of dietary fat, was striking.

Xanthoma diabeticorum is more than a dermatological curiosity. It dramatically calls attention to the disturbed fat metabolism which is a part of uncontrolled diabetes and which presumably plays a part in the high incidence of vascular disease accompanying diabetes mellitus.

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POLYCYTHEMIA VERA TERMINATING IN ACUTE LEUKEMIA

Report of a Case and Review of Literature

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and
ABRAHAM M. FRUMIN, M.D., Philadelphia

THE TERMINATION of polycythemia vera in acute leukemia is an infrequent occurrence. Because of the scarcity of such reports opportunity is taken to report one such case and to review others noted in the previous literature.

T. K., a 65-year-old white woman, was admitted to the Albert Einstein Medical Center, Southern Division, on March 20, 1953, because of weakness and pallor. She was known to have polycythemia vera since June, 1941, and was treated with venesections, x-rays, and P^{32} (Table). Physical examination revealed an elderly woman in acute distress. B. P., 130/70; pulse, 100; respiration rate, 20; temperature, 102 F. Marked pallor, purpura, and splenomegaly were noted. There was no icterus, adenopathy, hepatomegaly, or glossitis.

Blood studies showed RBC, 3,340,000; Hb., 9.7 gm.; reticulocytes, 0.9%; platelets, 140,000; WBC, 7400, with 1% segmented cells, 5% lymphocytes, 3% myelocytes, 3% promyelocytes, and 88% blast forms. A sternal marrow biopsy revealed a good preparation of a normocellular marrow. Erythropoiesis was normoblastic in nature, and erythrocytes occurred in markedly diminished numbers. Megakaryocytes were also diminished in number. The outstanding feature was the presence of increased numbers of blast cells, which constituted virtually the entire cell type, only occasional mature granulocytes being noted. As these blasts gave a peroxidase-positive stain, a diagnosis of acute granulocytic leukemia was made. The patient was treated with blood transfusions, antibiotics, and steroids without hematologic or clinical improvement. Death occurred on May 30, 1953, due to cerebral hemorrhage.

Submitted for publication June 23, 1955.

From the Departments of Medicine and Research, Albert Einstein Medical Center, Southern Division.

Clinical Data

Date	RBC, Million	Hb., %	WBC	Platelets	P^{32} (Oral), Mc.	
6/ 3/41	7.3	132	9,400	3,460,000	..	
7/ 7/41	7.3	132	10,400	.....	5	
1/ 6 42	8.0	150	11,700	.....	..	
4/23/42	8.3	130	13,700	.....	..	
10/23/43	10.0	125	10,200	.....	..	
4/27/44	8.0	105	11,400	.....	..	
8/ 1/44	12.3	130	10,400	.....	..	
10/13/44	10.0	125	9,200	.....	4	
1/13/45	5.8	95	9,000	.....	6	
6/14/45	4.4	85	6,400	.....	..	
10/30/45	4.5	85	6,800	.....	..	
2/ 5/46	5.0	95	8,400	.....	..	
9/18/46	5.2	100	8,900	.....	..	
7/ 8/47	6.7	115	6,100	.....	10	
2/23/49	5.0	95	8.400	.....	..	
9/12/49	5.1	102	9,700	.....	..	
2/20/50	6.3	130	9,700	Plentiful	8	
5/13/50	6.2	110	8,500	Plentiful	..	
10/15/50	6.7	120	8,000	Normal	..	
12/ 7/50	6.5	115	8,700	Normal	10	
7/ 3/51	5.8	112	9,800	Normal	..	
10/28/51	7.1	128	9,700	Normal	10	
12/10/51	6.5	115	8,700	Normal	..	
5/28/52	5.5	113	9,500	.....	8	Total 61
3/16/53	3.05	62	5,200	140,000	..	

COMMENT

A total of 34 cases of polycythemia vera terminating as acute leukemia has been found.* All were of the granulocytic variety. Two patients were treated solely with venesections,† whereas all the others received varying courses of x-rays, P^{32}, and venesections. It would therefore seem that acute leukemia may well represent the end-stage of some cases of polycythemia vera; the possibility of internal radiation (P^{32}) or external radiation (x-ray) accelerating this process cannot be too readily discarded. This was emphasized by Schwartz and Ehrlich [5] with specific reference to the chronic forms of leukemia.

The development of acute leukemia in our patient with polycythemia vera occurred after

* References 1-5 and Dameshek, W., cited by Wasserman.[3]

† Dameshek, W., cited by Wasserman.[3]

she had had the disease for 12 years. It has been estimated that the life expectancy for this disease is 10 to 15 years. It is readily apparent that the patient's life was not prolonged by the therapy she received. The total amount of P^{32} given over an 11-year period totalled 61 mc. Since this represented a comparatively large amount of internal radiation, the possibility of radiation-induced acute leukemia was raised. The additional factor of x-ray therapy over the long bones (total amount unknown) must also be considered.

It must be stressed that in six cases acute leukemia arose from a preexisting chronic granulocytic leukemia which had developed in patients with polycythemia vera. Two additional patients with chronic granulocytic leukemia developed a subacute variety, and these were also included in the total of 34 cases. The leukemic process in our patient was of the granulocytic variety, since the blast forms in the peripheral blood gave a positive peroxidase reaction.

The relative incidence of this complication varies with different hematologic centers. Wiseman [4] collected 453 cases of polycythemia vera and found 12 (2.7%) who died with acute leukemia. Wasserman [3] found 7 (11%) of the deaths in 64 cases of polycythemia vera to be due to acute leukemia. Stroebel [2] found that 4 (2.7%) of 148 cases of polycythemia vera died with acute leukemia. His series was included in Wiseman's total. Lawrence [1] collected 207 patients with polycythemia vera (121 were included in Wiseman's report) and found 8 (4%) who developed acute leukemia. All of these arose from a previously existing chronic granulocytic leukemia superimposed upon polycythemia vera.

The diagnosis of acute leukemia should be made only after careful examination of the peripheral blood and bone marrow. This is particularly true because it has been estimated [1] that 20% of patients with polycythemia vera have a leukemic blood picture. Moreover, as myelofibrosis with myeloid metaplasia and/or aplastic anemia are not unusual in the terminal stages of polycythemia vera, further difficulties would be expected to be encountered.

SUMMARY

A case of polycythemia vera terminating as acute leukemia is reported.

The importance of external (x-ray) and internal (P^{32}) radiation in the development of acute leukemia is discussed.

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News and Comment

ANNOUNCEMENTS

Course in Interpretation of Complex Arrhythmias.—A course in Interpretation of Complex Arrhythmias will be given at Michael Reese Hospital, Chicago, by Louis N. Katz, M.D.; Richard Langendorf, M.D., and Alfred Pick, M.D. This is an advanced course, intended only for experienced electrocardiographers. The class will meet daily from 9:00 a.m. to 5:00 p.m. Dec. 5-9.

Further information and a copy of the lecture schedule may be obtained from Secretary, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago 16.

American College of Surgeons Sectional Meetings for 1956.—The medical profession at large is invited to attend any of six Sectional Meetings of the American College of Surgeons, to be held in cities throughout the United States and Canada during 1956. Meeting cities are Jacksonville, Fla., Jan. 16-18; Philadelphia, Feb. 13-16; Milwaukee, Feb. 27-29; Colorado Springs, Colo., March 5-7; Little Rock, Ark., March 12-13; Edmonton, Alberta, Canada, April 23-25.

These meetings, like the five-day annual Clinical Congress, are designed for the purpose of disseminating information about new methods and therapies. In these programs the College draws on surgeons of outstanding ability, acting as teachers, to focus attention on problems encountered in day-to-day practice. Panels, symposia, papers, and medical motion pictures of greatest value to doctors practicing in the area are presented. What the surgeons want and whom they want to hear determines the programs, for these meetings are planned by Local Committees and aided by the College. Attendance at these Sectional Meetings grows each year, an indication of the modern surgeon's desire to keep informed.

Further information may be obtained from Dr. H. Prather Saunders, Associate Director, American College of Surgeons, 40 East Erie St., Chicago 11.

Cancer Lectures.—Northwestern University Medical School announces that its annual series of cancer lectures will be given from Oct. 12 to Nov. 23 for members of the medical profession. The lectures on research and present-day problems in cancer will be presented in the auditorium of the Veterans Administration Research Hospital, at 333 E. Huron St., from 5 to 6 p.m. on Wednesday evenings.

Dr. William Wartman, professor and chairman of the department of pathology at Northwestern University Medical School, is coordinator of the lectures.

The programs are as follows:

Oct. 12 The Pathology of Cancer of the Lung Correlated with Diagnosis, Treatment, and Prognosis
Dr. Lauren V. Ackerman
Washington University
St. Louis

Oct. 19 A Comparison of Adult, Embryonic, and Cancer Tissues
Dr. Harry S. N. Greene
Yale University School of Medicine
New Haven, Conn.

Oct. 26 Studies on the Mechanism of Hydrocarbon Carcinogenesis
Dr. Charles Heidelberger
University of Wisconsin
Madison, Wis.

Nov. 2 Present-Day Problems in Primary Lung Cancer
Dr. William E. Adams
University of Chicago Medical School
Chicago

Nov. 9 Recovery from Radiation Injury
Dr. Leon C. Jacobson
University of Chicago Medical School
Chicago

Nov. 16 Malignant Epithelial Tumors of the Extremities
Dr. Edwin A. Lawrence
Indiana University School of Medicine
Indianapolis

Nov. 23 The Role of Mutation in Relation to the Origin of Tumors
Dr. Walter J. Burdette
University of Missouri School of Medicine
Columbia, Mo.

Public Health Leaders to Evaluate Experience with Salk Polio Vaccine.—Evaluation of practical experience with the Salk polio vaccine by key figures in its development will be a feature of the 83d annual meeting of the American Public Health Association and meetings of 40 related organizations in the Kansas City, Mo., Municipal Auditorium, Nov. 14-18.

Participants in a panel discussion on Thursday afternoon, Nov. 17, will include Dr. Jonas E. Salk, University of Pittsburgh, who developed the vaccine; Dr. Thomas Francis Jr., University of Michigan, who directed evaluation of field tests which led to its adoption; Dr. Leonard A. Scheele, Surgeon General, U. S. Public Health Service; Dr. Hart E. Van Riper, Medical Director, National Foundation for Infantile Paralysis, and Dr. Robert E. DeFries, University of Toronto. The moderator will be Dr. Malcolm E. Merrill, Director of Public Health, Berkeley, Calif.

Dr. Herman E. Hilleboe, New York State Commissioner of Health and president of the American Public Health Association, will preside at the special session on polio, one of 75 scientific sessions scheduled.

Among topics to be emphasized are mental health, neighborhood planning, new approaches to chronic diseases, and experience with various medical care plans.

Course on Fluid and Electrolyte Balance.—A five-day program on fluid and electrolyte balance, under the chairmanship of Dr. George E. Burch, Professor of Internal Medicine, will be presented Jan. 16-21, 1956, through the Division of Graduate Medicine of Tulane University School of Medicine.

The course is planned as a review of the fundamental principles of water and electrolyte metabolism but will also emphasize the clinical applications of these principles. Frequent conferences and discussions at the bedside of patients will be held. Inquiries may be addressed to the Director, Division of Graduate Medicine, 1430 Tulane Ave., New Orleans 12.

European Symposium on Vitamin B_{12}.—Plans are being made for the first European symposium on vitamin B_{12} to be held the last week of May, 1956, in Hamburg. It will be under the auspices of the physiological chemist Prof. Kühnau and the internist Prof. Jores. The physiology and the clinical application of vitamin B_{12} in human and veterinary medicine will be discussed. For information write to Doz. Dr. H. Bauer, Nervenklinik, Hamburg-Eppendorf, Germany.

Fourth International Congress of Internal Medicine.—The Fourth International Congress of Internal Medicine will be held in Madrid Sept. 19-23, 1956, under the presidency of Prof. C. Jiménez Díaz.

There will be two main subjects, namely, "The Role of the Adrenals in the Pathogenesis and Evolution of Internal Diseases" and "Bronchial Asthma and Emphysema," each of which will be dealt with by a number of speakers. Communications on these themes or on any others of free choice will also be admitted.

Please address all inquiries to the Secretariat: Drs. J. C. de Oya and J. Gimena, Hortaleza n° 90.

Regular Corps Examinations for Medical Officers, United States Public Health Service.—A competitive examination for appointment of Medical Officers to the Regular Corps of the United States Public Health Service will be held in various places throughout the country on Nov. 15, 16, and 17, 1955.

Appointments provide opportunities for career service in clinical medicine, research, and public health. They will be made in the ranks of Assistant and Senior Assistant, equivalent to Navy ranks of Lieutenant (j. g) and Lieutenant, respectively.

Entrance pay for an Assistant Surgeon with dependents is $6,017 per annum; for Senior Assistant Surgeon with dependents, $6,918. Provisions are made for promotions at regular intervals.

Benefits include periodic pay increases, 30 days annual leave, sick leave, medical care, disability retirement pay, retirement pay which is three-fourths of annual basic pay at time of retirement, and other privileges.

Active duty as a Public Health Service officer fulfills the obligation of Selective Service.

Requirements for both ranks are U. S. citizenship, age of at least 21 years, and graduation from a recognized school of medicine. For the rank of Assistant Surgeon, at least 7 years of collegiate and professional training and appropriate experience are needed, and, for Senior Assistant Surgeon, at least 10 years of collegiate and professional training and appropriate experience are needed.

Entrance examinations will include an oral interview, physical examination, and comprehensive objective examinations in the professional field.

Application forms may be obtained by writing to the Chief, Division of Personnel, Public Health Service, Department of Health, Education, and Welfare, Washington 25, D. C. Completed application forms must be received in the Division of Personnel no later than Oct. 15, 1955.

Books

EDITED BY WILLIAM B. BEAN, M.D.

Management of Addictions. By Edward Podolsky, M.D. Price, $7.50. Pp. 413, with 24 figures and 13 tables. Philosophical Library, Inc., 15 East 40th St., New York 16, 1955.

Thirty-five papers from nineteen periodicals are collected under the editorship of Dr. Edward Podolsky in a volume entitled "Management of Addictions." This title would seem to suggest that the book offers a particular program or regimen for the treatment of narcotics addiction. Actually, however, more than two-thirds of the book is devoted to alcoholism, and the diversity of approaches reflected in the table of contents indicates that a specific treatment for either alcohol or drug addiction is still to be found. Although considerable basic information is contained in the individual papers, internists and general practitioners will probably be most interested in the respective papers by Diethelm and Pescor on "The Alcohol Problem" and "The Problem of Narcotic Drug Addiction." A number of the papers emphasize the importance of a multifactored approach to the understanding and treatment of both types of addiction. The family physician's understanding of the problems of addiction will be enhanced by reading the book, but it is questionable how much he will find which he can use directly in the treatment of the patients in his practice.

Included in the section on alcohol addiction are papers on psychodynamics, a pragmatic approach to control of chronic alcoholism, therapeutic success, the concept of genetotrophic disease, nutrition and alcoholism, recent advances in treatment, teamwork, psychotherapy, treatment with adrenal steroids and corticotropin, endocrine treatment, mephobarbital (Mebaral), aversion treatment, carbon dioxide maintenance therapy, calcium therapy, sedation with nonsedative drugs, Dimethylane, mephenesin (Tolserol), disulfiram (Antabuse), conditioned-reflex treatment, intravenous barbiturates, thiopental (Pentothal), and hypnotherapy. Among the papers in the section on drug addiction are reports on hypoadrenocorticism, group therapy, hospital treatment, calcium gluconate, prolonged sleep, diphenhydramine (Benadryl), and electroconvulsive therapy.

Unfortunately, the periodicals from which the papers are taken are given only blanket acknowledgement, and the specific sources of the individual papers are not indicated. Similarly,

the titles of the various authors are listed in a separate section entitled "Contributors" rather than with their papers. The value of the index is limited, because it is an author index and not a subject index.

Diabetes Mellitus in Infants and Children: Twelfth M & R Pediatric Research Conference. Edited by F. W. Haggness, Ph.D., M.D., with 15 participants. Price, free on request to the publisher. Pp. 79, with 23 figures. M & R Laboratories, Columbus 16, Ohio, 1955.

This report, a symposium on diabetes mellitus in infants and children, is the twelfth such symposium held on subjects of special interest to pediatricians since May, 1951. The brochure is sent as a public service to all members of the American Academy of Pediatrics and to any other physician desiring it.

Within the limitations of the time allotted to the conference and the size of the conference transcript this brochure is an excellent summary of the problems of juvenile diabetes. Fifteen participants took part in this symposium. The whole field of diabetes was covered briefly. The problems of need for continued research as to etiology are well summarized. When treatment is discussed the differences in management employed by various authorities are apparent, especially in the management of diabetic acidosis.

To the practitioner dealing with an occasional diabetic in his practice there would be much confusion in his mind as to the best thing to do in the way of fluid and electrolyte therapy. However, as a controversial segment of the subject the discussion is quite stimulating. Anyone reading the brochure completely will gain a better understanding of juvenile diabetes.

The Clinical Physiology of the Lungs. By Cecil K. Drinker, M.D., D.Sc. Price, not given. Pp. 84, with 27 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1954.

In a short monograph this well-known pulmonary physiologist presents in an informal and suggestive fashion the physiology of the lung as related to its special anatomical structure. The treatise is divided into five chapters. In the first chapter, the pulmonary artery system and the regulation of blood flow through this system is described. In the second chapter, the pulmonary veins and capillaries are discussed. The bronchi and bronchioles follow in the third chapter, with the discussion of the mechanism of asthma. Nervous innervation of the lung and its role in respiration, alveolar and bronchial function, and blood circulation follow next. Special attention is paid to neurogenic factors in pulmonary edema. Finally, the lymph circulation of the lungs is described.

This small book is comprehensive and stimulating. Much was contributed to the problem by the author himself. Very interesting, for instance, is the opinion that increased capillary pressure in the lungs by itself hardly leads to pulmonary edema. There are other factors involved, among which much is attributed to anoxia, leading to increased permeability of the alveolar epithelium. The book can be recommended to pulmonary and cardiac physiologists and also to clinicians interested in the field.

Cerebrovascular Disease. By James Peter Murphy, M.D. Price, $12.00. The Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1954.

This book, by a neurosurgeon, contains a large amount of concentrated factual information clearly presented and well illustrated. One-fourth of its pages is devoted to the embryology, anatomy, and physiology of the intracranial circulation. The remainder covers, systematically, the clinical varieties of cerebral vascular disease, including the vascular accidents of various origins, aneurysms and vascular tumors, venous sinus disease, hypertensive encephalopathy, inflammatory and collagenous diseases, blood dyscrasias, and a discussion of headache. The chapters on differential diagnosis of the acute cerebral vascular accident, on cerebral thrombosis, on subarachnoid hemorrhage, and on the general management of the patient are particularly commendable. There is a brief discussion of diagnostic and therapeutic techniques, the latter involving surgical procedures of interest largely to the neurosurgeon.

The author has produced a good synopsis, with a reasonable balance between basic knowledge, clinical findings, and practical application of both in diagnosis and treatment. At times, however, the description of important clinical conditions is tantalizingly brief. For those who are interested, more complete information can be found in the bibliography, which is adequate. This volume will serve a very useful purpose to medical students and physicians who want a survey of this important field of disease.

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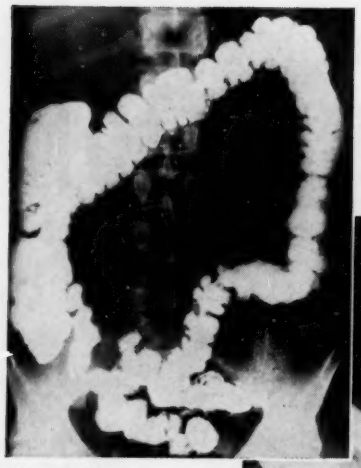

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1. Sebrell, W. H.: Developing Modern Nutrition Programs, Public Health Reports, United States Department of Health, Education, and Welfare 69:277 (Mar.) 1954.
2. Jolliffe, N.: The Pathogenesis of Deficiency Disease, in Jolliffe, N.; Tisdall, F. F., and Cannon, P. R.: Clinical Nutrition, New York, Paul B. Hoeber, Inc., 1950, p. 22.
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4. Goddard, V. R., and Marshall, M. W.: The Calcium Content of Commercial White Bread, United States Department of Agriculture, Technical Bull. 1055, 1952.
5. Sherman, H. C.: Chemistry of Food and Nutrition, ed. 8, New York, The Macmillan Co., 1952, pp. 212, 599.

The nutritional statements made in this advertisement have been reviewed and found consistent with current medical opinion by the Council on Foods and Nutrition of the American Medical Association.

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For each of these patients, he made the same diagnosis: depression.

Watts found—as countless other physicians have discovered—that when he specifically treated these patients for depression, their miscellaneous psychosomatic complaints vanished.

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